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# Five Cases (Three in Siblings) of Idiopathic Hypoparathyroidism Associated with Moniliasis[1]

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VERY little exact information is available on the etiology of idiopathic hypoparathyroidism. Since there are normally four parathyroid glands, the question arises as to what phathologic influence could exert itself in all four areas. *A priori* the loss of some trophic hormone, the presence of some circulating toxin with a specific affinity for parathyroid tissue, or the predilection on the part of the parathyroid glands for some infection (cf. adrenal glands and tuberculosis) might produce atrophy or destruction of all four glands. The authors know of on y two cases of undoubted idiopathic hypoparathyroidism to come to autopsy. As recorded in a previous paper from this clinic (1), the post mortem of a boy who died with idiopathic hypoparathyroidism showed complete aplasia of the epithelial cells of all four parathyroid glands with replacement by fat cells but with retention of the capsules. Cantarow, Stewart and Morgan (2) were unable to find parathyroid tissue in a patient with idiopathic hypoparathyroidism who died. In the hope of shedding further light on the etiology of idiopathic hypoparathyroidism there are reported here three cases in one family, of which at least two, and probably three, were complicated by moniliasis; two other case reports in which idiopathic hypoparathyroidism was associated with moniliasis are included.[2]

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[2] Since this paper was submitted for publication Dr. Elmer L. Sevringhaus has kindly called the attention of the authors to a case of idiopathic hypoparathyroidism reported

## CASE HISTORIES

*Case 1. Angelo G.*, M. G. H. #346719, a 12-year-old school boy of Italian ancestry, was admitted to the Massachusetts General Hospital on April 20, 1942 because of seizures of 2 years' duration.

At the age of 10 he began to have simple "fainting spells" without convulsions in which he would lose consciousness for a few seconds. These attacks consisted generally of momentary inattentiveness. At first, over a period of months, they came on about once a week; then for several months he was free of them entirely.

FIG. 1. Nail changes in case 1. Note that toenails are not involved except for moderate hypoplasia.

About 1 year before entry he began to exhibit stiffness of the right leg and arm during the attacks. Three months before entry the attacks began to occur about 4 or 5 times daily and were accompanied by convulsive movements of the right arm and leg. The patient could tell when the attack was coming but could not describe definite aura. He was not completely unconscious during a seizure but could hear what was going on about him and answer questions which had been repeated several times. He never bit his tongue nor lost sphincter control. Immediately following the attacks he felt "lazy." He never experienced headaches, visual disturbances, dizziness, nausea or vomiting. There was no weakness of the right side of the body between attacks.

*Family history.* The mother and father are first cousins. The mother has gall stones, and a stone in her right kidney, but the etiology of the stones is not hyperparathyroidism as judged from the normal serum calcium and phosphorus levels. The father has an enlarged spleen and blood findings characteristic of hypochromic polycythemia. Of the 6 living siblings, the only two examined likewise have hypochromic polycythemia (see table 1). Two sisters (see cases 2 and 3) died at 13 and 14 years, respectively; both of these also had hypochromic polycythemia, one was said to have had tuberculosis. One brother died at 3 following an operation for bone infection, another died at 1 month from "pneumonia."

*Past history.* The patient was born at term without difficulty and developed in a "normal fashion." Since infancy the nails of the hands but not of the feet were deformed. The changes were first noted in the nails of the thumbs. More recently, because of onychophagia, the deformities have become more marked (fig. 1). Except for measles at the age of 2, there were no childhood diseases. Tonsillectomy was performed 3 years before entry; there were no other operations or injuries.

*System review.* Non-contributory.

*Physical examination* revealed a rather thin but fairly healthy appearing young boy. The skin was dry with prominent hair follicles; all of the fingernails of the hands were irregular, with pitted deformities (fig. 1); the toenails were normal. The fundi were markedly congested and there was tortuosity of the retinal vessels with blurring and elevation of the disks but without hemorrhages or exudate. As shown by examination with the slit-lamp, there was one small opacity in the anterior cortex on the left lens which was not necessarily suggestive of parathyroid deficiency. Fissuring and a slight whitish exudate were observed at the corners of the mouth. The tongue was rather smooth. The heart and lungs were normal, and the blood pressure 100/60 mm. Hg. The liver and spleen were not palpable. There was complete absence of all deep reflexes. The abdominal and Babinski responses were normal. The visual fields were full.

*Laboratory data.* The authors are indebted to Dr. Burdick G. Clark for the following hematological

by him, in which monilia albicans was recovered from mouth lesions on two occasions. (Sevringhaus, E. L.: *Am. J. Med. Sci.* 203: 726. 1942). This patient was seen at the age of 21. The tongue and mouth lesions were first noted at the age of 4, whereas the symptoms of tetany did not begin until the age of 5.

studies. The indices were made on heparinized blood. The blood smear showed hypochromia, microcytosis with significant variation in size and shape and with elongated, very small and tear-drop forms. The platelets were normal in appearance. The hemoglobin was 11 gm. per 100 cc. (Sahli); the red corpuscle count, 5.9 million; hematocrit, 35; color index, 0.635; volume index, 0.734; mean corpuscular volume, 62.3 (normal =87.0). The mean corpuscular hemoglobin was 18.6 normal, 29.5). The mean corpuscular hemoglobin concentration was 29.9 (normal, 32.9). The white corpuscle count was 9,600 and a differential showed polymorphonuclear neutrophils, 86 per cent; lymphocytes, 10 per cent; large mononuclear leukocytes, 2 per cent; polymorphonuclear eosinophils, 2 per cent. There was free hydrochloric acid in the gastric contents after histamine administration. The pH of the urine was 5.5; the specific gravity, 1.018; albumin, none; sugar, none; the amount of sediment was normal. The Hinton reaction was negative. At lumbar puncture the initial pressure was 170, the final pressure 120 mm. of $H_2O$, free dynamics, with a total protein of 21 mg. per 100 cc. The spinal fluid Wassermann reaction was negative. The gold sol curve was normal. An electroencephalogram made during attacks was grossly abnormal but there was no evidence of localization. Cultures of scrapings from the fingernails were made on Sabouraud's media by Dr. Burdick G. Clarke and showed a good growth of monilia (?albicans).

Subsequently, Dr. Jacob H. Swartz of the Dermatological Service saw the patient in consultation regarding the fingernails. He wrote: "I cannot make a diagnosis on the fingernails alone. In this case some look like psoriasis, others like fungus, and still others atypical of both. I note that the toenails are not involved. The patient shows, however, red patches covered with whitish exudate scattered over the roof of the mouth and buccal mucosa. He also shows scaling, fissuring and redness at the corners of the mouth and some redness and scaling in the webs of the fingers. Microscopic examination of the scrapings from the nails were negative, but scrapings from the mouth showed a good many hyphae, septate mostly and some budding and non-budding yeast cells. Because of the mouth findings, one must suspect moniliasis. It may, however, be a superimposed condition upon a metabolic disorder." Cultures were taken, after which Dr. Swartz made the following report: "The organism obtained on the culture from the mouth is a monilia albicans. Nails did not grow a similar organism." From a later culture from the nails monilia was grown.

*Roentgenograms.* An intravenous pyelogram with diodrast revealed normal findings. The skull sutures were wider than normal and the convolutional markings were slightly prominent. The epiphyseal development was normal for the patient's age and the degree of calcification of the bones was not abnormal.

*Course in hospital.* The patient received no medication during the first 11 days in the hospital and had over 20 attacks. Six of these were observed and consisted of generalized tonic and clonic convulsions, with coma but without loss of sphincter control. The attacks lasted 10 to 20 minutes and were followed by stupor of variable duration up to one-half of an hour. Four days before discharge, the patient was placed on anticonvulsive therapy and had no seizures during that period. He was discharged on May 12, 1942.

*Second admission.* The patient was readmitted on July 2, 1942, because of the recurrence of seizures, nausea, vomiting and drowsiness. The seizures now involved only the right leg and lasted from 2 to 8 hours. Neurological findings were unchanged. A lumbar puncture performed with the patient well relaxed demonstrated increased intracranial pressure (initial pressure 250 mm. of $H_2O$). In view of the choked disks, increased intracranial pressure, convulsive seizures and lack of localizing findings, ventriculograms and encephalograms were made but no suggestive findings were obtained.

Fortunately a case of 'pseudo-hypoparathyroidism' (*vide infra*) was under observation at the time, whose history somewhat paralleled that of the patient; furthermore, the case records of the sisters (cases 2 and 3) were obtained and diagnosis noted. With these considerations the patient was re-examined and was found to have a strongly positive Chvostek's sign bilaterally. Accordingly the indicated serum chemical determinations were made: the serum calcium was very low, 4.7 mg./100 cc. and the serum phosphorus very high, 9.3 mg./100 cc.; the serum phosphatase level, 7 Bodansky units, was relatively normal for the age.

*Response to therapy.* The patient responded in the usual fashion to dihydrotachysterol therapy; the serum calcium rose to normal levels while the serum phosphorus fell, although not quite to normal. The patient's mental alertness returned and there were no further convulsive seizures. Chvostek's sign disappeared. A lumbar puncture 13 days after treatment showed a return to normal dynamics with an initial pressure of only 150 mm. of $H_2O$. The Q-T interval fell from a high normal to a normal value. There was little immediate change in the optic fundi and the deep reflexes remained absent. The patient was discharged on his 45th hospital day completely asymptomatic and mentally quite alert.

There was no recurrence of seizures five months after discharge. The nail findings and the mouth lesions remained unchanged, but all papilledema disappeared, and the knee jerks and ankle jerks returned. The patient returned to the normal active life of a school boy.

*Case 2. Lucy G.*, M. G. H. #311509, was a 5-year-old Italian girl who was admitted to the Children's Medical Out-Patient Department on July 31, 1930, because of white patches in the mouth of 3 years' duration. Another sister (case 3) was said to have the same condition. Examination at that time revealed a well developed and well nourished young girl. Her tongue, gums,

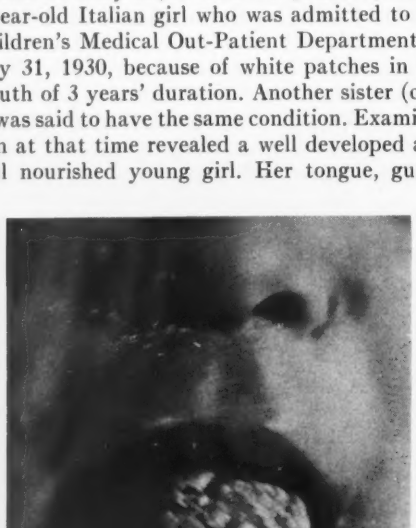

FIG. 2. Tongue of case 2. Note lesions around nose as well as those on tongue.

and inner sides of the cheeks were covered with thick white patches. The lips were fissured at the corners. The tonsils were enlarged and red. Two or three teeth were slightly carious. A few small cervical glands were palpable bilaterally. Examination of the heart, lungs and abdomen revealed normal findings. Tuberculin tests were negative at dilution of 1/1000. Treatment consisted of general hygienic measures and local irrigations but the condition became progressively worse.

On Jan. 27, 1931, the patient was admitted to the hospital because of paroxysms of laryngospasm of one month's duration. On Christmas Day, after playing out of doors for several hours, the child returned home complaining of pains in the legs. She was put to bed and that evening had her first attack. It was described as being a "fit" in which she became stiff all over and twitched at various parts of her body, particularly the hands and feet. At times she would almost choke to death, get blue, struggle and writhe because of inability to get her breath. The spell lasted for 5 or 10 minutes, only to recur a short while later. The following day she developed a head cold and a rash appeared on her body. This was diagnosed as measles by her physician and subsequently 3 other children developed measles. She continued to have frequent spasms of the hands, feet and larynx but not of the alarming nature of the initial attack. One day before admission, however, the attacks became quite frequent and the choking spells which came every few minutes held the entire family in terror.

*Past history.* The patient was born at full-term with a normal delivery. She was breast fed for one year and received no cod liver oil or orange juice. At the age of 2 the patient was noted to have white spots in her mouth. These were of minor concern until 6 months before admission when they became so marked that treatment was sought from her local physician. Nine months before admission the patient developed a large mass in her neck which was incised and drained of pus by her local physician. Cramps in her legs and arms were complained of at the time, but sore throat was denied. There were no other illnesses in the past history.

*Family history.* See *case 1.*

*Physical examination* revealed a well developed and fairly well nourished child who was quite excitable and had paroxysms of coughing with crowing inspiration and difficulty in breathing. The skin was dry and rough with prominent hair follicles. There was, however, marked perspiration with excitement. Fissures with whitish deposits were observed at the angles of the mouth. The tongue and buccal mucous membranes were covered with scattered, irregular, grayish white, slightly elevated patches which had a milky appearance (fig. 2). The teeth were slightly carious. There were tender glands in the anterior and posterior triangles of neck. Scattered sonorous râles were present bilaterally in the lungs. The nails of the right thumb and of the left second finger were deformed and thickened. No tendon reflexes were obtainable. The abdominal and plantar reflexes were normal. Trouseau's and Chvostek's signs were strongly positive. Lenticular opacities were sought for and were not found.

*Laboratory data.* The urine was acid with a specific gravity of 1.020. There was no albumin and rare white blood cells were observed. The hemoglobin (Sahli) was 85 per cent; the red blood corpuscle count 5.97 million. The leucocyte count was 11,800. A blood smear showed "slight variation in size and shape of red blood cells." An examination of the stools showed them to be alkaline and the guaiac test for occult blood was negative; no parasites were detected. The serum calcium was 5.6 mg./100 cc.; the serum phosphorus, 8.9 mg./100 cc.; the Wassermann reaction was negative. The tuberculin test was negative in a dilution of 1/1000. Excretion of phenolsulphonphthalein was greater than 60 per cent in 2 hours. The $CO_2$ combin-

ing power was 20.6 m. eq. per liter (later 27.0 m. eq. per liter). A test of electrical reactions showed a cathodal closing contraction of less than 1 m. amp.; an anodal closing contraction of 2.5 m. amp.; an anodal opening contraction of 1.5 m. amp. and a cathodal opening contraction of 4.2 m. amp. The B.M.R. was +10 per cent. Scrapings from the mouth and nail cultured on Sabouraud's media were positive for 'yeasts.' Mycelia were found on mouth scrapings.

*Roentgenograms.* Examination of the teeth, long bones and chest revealed no abnormalities.

*Course in hospital.* The thrush was treated vigorously with ethyl iodide inhalation, mouth washes, Kromayer lamp and debridement without benefit. The patient continued to have frequent attacks of laryngospasm and carpopedal spasm which subsided somewhat under therapy with calcium chloride and viosterol. While the patient was on the ward she developed conjunctivitis and right otitis media which were successfully treated. The patient was discharged on April 24, 1931, because of the presence of infectious disease on the ward. She did fairly well for 3 months but was readmitted on July 24. 1931, because of the recurrence of symptoms. The serum phosphorus at that time was 9.0 mg./100 cc. The patient was discharged one week later. On Aug. 1, 1931, she had a slightly different type of attack in which she suddenly lost consciousness, clenched her fists and had convulsive twitching of the face and extremities for one-half of an hour. She was readmitted to the hospital. The serum calcium level was 5.5 and the serum phosphorus was 9.0 mg./100 cc. Findings in the urine examination were normal. She was given parathyroid hormone, 30 units daily, for one week. The serum calcium rose to 8.6 mg./100 cc., while the serum phosphorus level is recorded as having risen to 10.4 mg./100 cc. The mouth and nail lesions remained unchanged. The patient was discharged free of tetany on Sept. 19, 1931. The last clinic visit was on Feb. 2, 1933, at which time the tongue appeared as if covered with thick paste. The Trousseau and Chvostek signs were positive. Attacks of tetany continued to occur about every 3 months but the child managed to continue in school. At the age of 14 the child is said to have developed a urinary shut-down and she "swelled up all over and died." There was no autopsy.

*Case 3. Lorenza G.*, M. G. H. #305594, was a 12-year-old girl who entered the Massachusetts General Hospital on March 27, 1930, because of spasms of the hands and feet.

The patient was "healthy" until 2 years previously when she was knocked unconscious by an automobile. She did not regain consciousness for 3 days and remained at the hospital for a month. After discharge she failed to gain strength normally, seemed tired, lacked ambition and any desire to play. Her appetite was quite poor. The patient, however, kept up in her school work. These symptoms continued without progression until 6 months before admission when the patient had her first attack of carpopedal spasm which lasted for 3 days. The seizures cleared up gradually and no more attacks occurred until 6 weeks later, but during the 3 months before entry the attacks occurred about every 10 days.

*Past history.* The patient was born at full-term with normal vertex delivery. She gained well and was breast fed. She had her first tooth at 8 months and walked and talked at 1 year. At the age of 3 years she had measles and at 4 whooping cough. She was in bed one month at the age of 7 with a cough and cold, and one quart of clear fluid is said to have been drawn off the chest. The nail changes (*vide infra*) developed at the age of 4 to 5, according to the present statements of the parents. The dietary history revealed no abnormalities.

*Family history.* See *case 1.*

*Physical examination* revealed a normally developed but poorly nourished child. There was carpopedal spasm. The skin was dry and scaly, the hair thin and sparse. The eyebrows were absent. The nails of the hands were 'hyperkeratotic.' The conjunctivae were dull red and small 'phlyctenules' were present in both eyes in the region of the limbus. There was a photophobia which resulted in a continual squint. The teeth were quite dirty and the upper mid-incisor and lower canine teeth were missing; the remaining teeth were irregular in shape. The tongue and buccal mucous membranes were covered with small ulcerations and there was a thick white membrane which wiped off readily leaving a dark red mottled base. The thyroid was not palpable. Numerous fine and coarse râles were heard throughout both lungs. The spleen was not palpable. The deep reflexes were absent. The Babinski sign was negative. The blood pressure was 102/76 mm. Hg.

*Laboratory data.* The findings in the urine examination were normal. The red corpuscle count was 5.6 million with a hemoglobin (Sahli) of 75 per cent. A blood smear showed moderate achromia with slight variation in size and slight polychromatophilia and with normal appearing platelets. The serum calcium was 7.0 mg./100 cc.; the serum phosphorus, 5.0 mg./100 cc. The tuberculin test, made at a dilution of 1/1000, was strongly positive. The Wassermann reaction was negative. At lumbar puncture the initial pressure was 220 mm. of water; otherwise the spinal fluid was normal. The excretion of phenolsulphonphthalein was 60 per cent in 2 hours. A test of electrical reactions (Erb's sign) showed a cathodal closing contraction of 1.0 m. amp.; an anodal closing contraction of 3; an anodal opening of 1.5 and a cathodal opening contraction of 3.0 m. amp.

*Roentgenograms.* The skull was unusually large. The convolutional markings of the brain were quite prominent. The chest plate was negative except for enlargement of hilus shadow. The pelvic bones were considerably atrophied.

*Course in hospital.* Without specific therapy, the serum calcium rose to 8.0 mg./100 cc. and the serum phosphorus level fell to 4.4 mg./100 cc. While the patient was receiving irradiated ergosterol therapy the serum calcium rose to 10.0 mg./100 cc. and the serum phosphorus remained stationary at 4.4 mg./100 cc.

Dental consultants felt that the oral condition was thrush in spite of negative smears for yeasts. Unfortunately no cultures were taken. The oral sepsis was resistant to all modes of therapy (extraction of the teeth, sodium perborate, irrigation). Dr. Jacob H. Swartz expressed the opinion that the loss of hair and eyebrows and the condition of the nails strongly suggested some trophic disturbance or mycotic infection.

Toward the end of the hospital stay the patient's blood pressure ranged around 70/45 to 70/55 mm. Hg. The mouth, when examined for pigmentation, had scattered areas of dark pigmentation over the soft and hard palate. The skin was noted to be darker than that of the parents or siblings.

The diagnoses on discharge from the hospital were: hilum tuberculosis, phlyctenular conjunctivitis, tuberculosis of adrenal glands with Addison's disease, thrush, and tetany resulting from poor calcium absorption. The patient was referred to the North Reading Tuberculosis Sanitarium where she remained 3 weeks. She lost weight rapidly, refused to eat and was taken home at the insistence of her parents, where she rapidly declined and died 3 weeks later. There was no autopsy.

*Case 4. E. R.*, B. H. #431088, the daughter of impecunious Porto Rican parents, was born normally at term, weighing approximately 7 lb. She was the youngest of 9 children; the others were alive and presumably in good health. She was fed at breast for 3 months and in what was probably an irregular fashion thereafter. Cod liver oil was not given until the fifth month and rickets made its appearance. The child developed normally. She had pertussis at 14 months and first came under the care of the Babies Hospital at 20 months because of otitis media, mild rickets and severe nutritional anemia. During the course of this illness a few patches of whitish exudate were seen in the pharynx but a smear for thrush was negative; a culture was not made. She was again in the hospital when 26 months old because of lobar pneumonia due to pneumococcus, type 2, and bilateral otitis media from which pneumococcus, types 2 and 19, were recovered. A third admission was required one month later because of a staphylococcus infection of the chin. She contracted scabies when about 4 years old and except for one brief remission following intensive treatment, this has persisted up to the present time. At the age of 7 years the child had a brief episode of unexplained fever. A month later she entered the hospital for the fourth time because of the sudden appearance of an evidently inflammatory swelling just above the left sternoclavicular articulation. Roentgen examination failed to reveal the source of suppuration. Aspiration of the abscess yielded yellow, blood-tinged material the direct smear of which contained no organisms; culture for aerobic and anaerobic bacteria and for the tubercle bacillus remained sterile. Examination of the blood serum for agglutinins against a representative number of pathogens also yielded negative results. The Mantoux test with 0.1 mg. of tuberculin was negative.

Six months later, when the child was 7.5 years old, she began to complain of pain in the elbows, shoulders, knees and wrists and said that her hands were stiff. A week later her mouth became sore. Smears showed no monilia but contained many fusiform organisms and a few spirillae. Two days later she had a generalized convulsion with alleged loss of consciousness lasting 10 minutes. After five more convulsions and several attacks of vomiting during the next 3 days the child entered the hospital for the fifth time.

Physical examination revealed an undersized, thin girl with scabies and diffused stomatitis; the features of the latter suggested that it was of the aphthous or herpetic variety. In the lens of the right eye there were a few small opacities which were evidently of congenital origin. The nails of the right index finger and of the left thumb were somewhat thickened, very irregular and brittle. The other nails of the hands and those of the feet appeared normal.

The cause of the convulsions remained unclear until three days after entry when one occurred which was accompanied by carpopedal spasm. The serum calcium was found to be 4.8 and the inorganic phosphorus 9.1 mg./100 cc. and the alkaline phosphatase activity 6.3 Bodansky units. The serum bicarbonate was 23.5 and the chlorine 97.4 m. eq. per liter; the pH was 7.43 at 38° C., measured with the glass electrode. The total protein was 7.21 gm., the albumin 4.26 and the globulin 2.96 gm./100 cc. The serum cholesterol was 136.4 mg./100 cc. and the whole blood non-protein nitrogen 32.4 mg./100 cc. These values are representative of many which were obtained subsequently. The only additional chemical datum which needs to be recorded is an inulin clearance of 61.3 cc. per minute, equivalent to a normal value of 112.8 cc. per minute per 1.73 square meters, the standard surface of reference for clearance tests. The hemoglobin was 11.2 gm./100 cc. and the red blood cell count 3.84 million; the color index was 1.01. The urine was normal. Roentgen films of the entire skeleton revealed normal mineralization and no evidence of disturbed ossification at the epiphyses. Pathologic calcification was not evident in the region of the parathyroids or of the kidneys. Roentgenograms of the teeth failed to

contribute significant information. The Q-T interval of the electrocardiogram was prolonged to between 0.36 and 0.38 seconds. An electromyogram showed increased excitability of the nerves. Chronaxie was increased from 3 to 4 times normal in 12 nerves which were tested. A smear from the mouth showed only spirochetes and fusiform organisms. Culture of the deformed fingernails on three occasions consistently resulted in a growth of monilia albicans.

Symptoms of tetany abated promptly and the values for serum calcium and phosphorus returned to normal with the use of calcium chloride by mouth, initially in doses of 6 gm., then 3 gm., and finally 1 gm. daily. Subsequently calciferol in doses of 100,000 U.S.P. units daily was used for several weeks with good results. For the last 18 months the child has received no treatment. She eats a diet of unsupervised composition. While both the serum calcium and the inorganic phosphorus remain in the neighborhood of 5 mg./100 cc. and Chvostek's sign is consistently positive, the child has had neither subjective discomfort nor spasms except of mild degree and transiently in association with acute infections.

*Case 5. S. A. H.*, B. H. #667161, a white girl, one if two siblings, was born at term by difficult forceps delivery. Breast feeding was practiced for only a short time and then cow's milk formulas were given. The child received no cod liver oil during infancy. Development was normal. She had chicken pox at 9 months, measles at 1 year and pertussis at 3 years. The whooping cough was severe and generalized convulsions occurred almost daily for 2 or 3 weeks at the height of the illness. Throughout the following year these took place about once a month but lasted only a few seconds; they ceased after tonsillectomy at the age of 4 years. When the child was 6 years old she suddenly manifested carpopedal spasm unaccompanied by other symptoms. The serum calcium was 6.4 mg. and the carbon dioxide combining power 57 vols./100 cc. The whole blood sugar was 99 mg. and the nonprotein nitrogen 25 mg. Carpopedal spasm disappeared rapidly in response to the oral administration of 4 gm. of calcium gluconate daily. At this point the child entered the Babies Hospital for further investigation.

The only physical features of interest were a positive Chvostek's sign and peroneal reflex, extreme dental caries and a lesion of the nail of the index finger of the right hand. The nail was thickened, transversely ridged and brittle. The other nails of the hands and feet were not affected. Chemical examination showed the serum calcium to be 7.0 mg./100 cc., inorganic phosphorus 10.5 mg., alkaline phosphatase activity 4.3 Bodansky units, bicarbonate 26.5 m. eq. per liter, chlorine 101.6 m. eq., total protein 6.80 gm./100 cc. and the pH, determined at 38° C. with the glass electrode, 7.53. Nonprotein nitrogen was not measured. However, the average of 4 determinations of the renal clearance of endogenous creatinine, made by the technique of Popper and Mandl (3), was 141 cc. per 1.73 square meters of body surface per minute, a value which demonstrates normal glomerular filtration. The hemoglobin was 13.1 gm./100 cc. and the red blood cell count 4.18 million per cu. mm.; the color index was 1.08. Urinalysis revealed normal findings. The Mantoux test with 0.1 mg. of tuberculin was negative. The Q-T interval of the electrocardiogram was 0.25 seconds on one occasion and 0.29 on another. Chronaxie was much prolonged in a representative number of muscles. Roentgen examination of the entire skeleton, of the neck and of the kidneys demonstrated only normal details. Dental films showed normal calcification of the erupted teeth. The enamel of the unerupted bicuspids appeared somewhat hypoplastic. Culture of the deformed fingernail resulted in a growth of monilia albicans. The child was treated for several weeks with aluminum hydroxide gel without effect on the concentration of serum calcium and inorganic phosphorus. She has remained under medical observation for a period of 16 months. Although the calcium level remains in the neighborhood of 7.5 mg./100 cc. and the phosphate at about 10 gm., there have been no further episodes of carpopedal spasm, no subjective discomfort and no convulsions. The only overt evidence of tetany is increased susceptibility of the facial nerves to mechanical stimulation.

## DISCUSSION

*Multiple cases of hypoparathyroidism in one family.* The authors have been unable to find in the literature any conclusive instance of multiple cases of idiopathic hypoparathyroidism in one family. Von der Heydt (4) reported a family of 8 children of German-Polish extraction of which 3 developed cataracts at the ages of 11, 21 and 12, respectively. None of the siblings was stated to have had symptoms of tetany or signs of ectodermal dysplasias, but the blood chemical determinations were somewhat suggestive of mild parathyroid deficiency (case A, 11 years old: calcium 9.25, phosphorus 4.4 mg./100 cc.; case B, 21 years old: calcium 8.9, phosphorus 4.5 mg./100 cc.; case C, 12 years old: calcium 7.6, phosphorus 4.7 mg./100 cc.). In his discussion, von der Heydt refers to 4 siblings with cataracts studied by Dr. S. Gifford.

*Relation of moniliasis to hypoparathyroidism.* Except for a very recent paper by our pediatrics colleagues, Talbot, Butler and McLachlan (5), the association of hypoparathyroidism with moniliasis, to our knowledge, has not been previously reported. The nature of the relationship between the two conditions is of prime interest. Four questions seem worthy of discussion:

1. Are the two conditions totally unrelated?
2. Does the moniliasis cause the hypoparathyroidism?

3. Does the hypoparathyroidism predispose the individual to moniliasis?
4. Finally, are both the moniliasis and the hypoparathyroidism the result of a third abnormality?

That the hypoparathyroidism and the moniliasis in cases 1, 2 and 3 were not totally disconnected phenomena is suggested by the family history. One is not surprised to find the presence of multiple cases of an infectious disease in one family. One does take notice, however, when one finds a family of 10 children with 3 cases of an infectious disease and with these very 3 cases complicated by an extremely rare disease, idiopathic hypoparathyroidism! This plus the two additional cases from the Babies Hospital in which these two rare conditions were associated make it most unlikely that this association is coincidental. Furthermore, Talbot, *et al.* (5), have studied 2 siblings in whom moniliasis was associated with deficiency of another gland of internal secretion, namely, the adrenal cortex; furthermore, one of these two patients is thought to have idiopathic hypoparathyroidism as well.

To digress for a moment from the main trend of thought, it is of interest that case 3 was also thought to have had Addison's disease on a tuberculous basis. One of the patients reported by Talbot, *et al.*, did come to autopsy; this was the case which did not have idiopathic hypoparathyroidism; the adrenals showed the so-called 'atrophied' type of pathology, not tuberculosis.

Is the moniliasis the cause of the hypoparathyroidism? That it preceded the parathyroid insufficiency in cases 1, 2 and 3, and hence might have been the cause of the insufficiency but not the result, is suggested by the time relationships in the evolution of symptoms and by the absence of certain dental disturbances (*vide infra*).

In case 1 (*Angelo G.*) the dystrophy of the nails antedated the onset of clinical symptoms by at least 10 years. In case 2 (*Lucy G.*) the onset of 'thrush,' which was later identified as due to monilia, occurred 3 years prior to the onset of tetany. In case 3 (*Lorenza G.*) the nail changes developed at the age of 4 or 5, whereas the tetany did not appear until the age of 11. The diagnosis of moniliasis in this case was not established by culture but such findings as the hyperkeratotic nails, the conjunctivitis, the stomatitis and cheilitis, and the history in the siblings make such a diagnosis most likely.

Furthermore, roentgenograms of the teeth in cases 1 and 2 furnish additional evidence that the hypoparathyroidism had been of relatively short duration as compared with moniliasis. Albright and Strock (6) found that hypoparathyroidism in children is accompanied by retarded development of those parts of the teeth which form after the onset of the condition. Although the roentgenograms in case 1 showed definite retardation in the development of the teeth, the changes were not sufficiently extensive to suggest that the hypoparathyroidism had been present for 10 years. The roentgenograms of the teeth of case 2 (*Lucy G.*), whose 'thrush' began at the age of 2 are no longer available, but the record contains a statement by one of us (F.A.) to the effect that the normal appearance of the teeth then at the age of 5 was against long-standing hypoparathyroidism.

Could the moniliasis be the result of the hypoparathyroidism? This possibility must at least be mentioned. All the evidence stated above suggests that the hypoparathyroidism followed the moniliasis. Furthermore, the fact that, to the authors' knowledge, no instance of moniliasis following post-operative hypoparathyroidism has been reported, makes this supposition most unlikely. Yet, as will be discussed below, hypoparathyroidism does give rise to widespread ectodermal disturbances (see case 3) which might, in certain cases, predispose the individual to moniliasis.

A fourth possibility is that both the hypoparathyroidism and the predisposition to moniliasis may have been the result of some third factor, such as an hereditary defect in the germ plasm. To support this contention is the fact that the father and mother of cases 1, 2 and 3 are first cousins, and that in cases 1, 2 and 3, the father, and at least two of the siblings have a congenital blood dyscrasia, which can be classified under the name of "Familial Mediterranean Target-Oval Cell Syndrome." This term was introduced by Damashek (7) and includes a number of closely related conditions among which are Cooley's anemia and the condition under discussion here which might be called congenital hypochromic polycythemia. Damashek gives as the common denominator of the various dyscrasias thus grouped together, "a reduction in the hemo-

globin level, hypochromia, abnormality of the red cells including the presence of target cells, oval cells, stippled cells, increased hypotonic resistance and complete refractoriness to iron therapy." The conditions apparently are confined to individuals of Mediterranean heritage; for this reason Whipple and Bradford (8) introduced the term, "Thalassemia."

The hemoglobin values and red counts of cases 1 and 3 and of the father and mother and of two of the siblings are recorded in table 1. A careful study of the blood findings of case 1 was made by Dr. Burdick G. Clark and is recorded in the case history (*vide supra*).

TABLE 1. DATA RELATING TO THE HYPOCHROMIC POLYCYTHEMIA PRESENT IN CASES 1, 2, AND 3, THEIR FATHER, AND TWO OF THEIR SIBLINGS

| Name | Hgb., Sahli | Erythrocytes | Color Index | Leukocytes |
|---|---|---|---|---|
| | *gm.* | *million* | | |
| Mr. G. | 12.5 | 5.83 | 0.8 | |
| Mrs. G. | 15.1 | 5.04 | 0.9 | |
| Angelo (case 1) | 12.5 | 5.87 | 0.6 | 9,600 |
| Lucy (case 2) | 14.0 | 6.03 | 0.7 | |
| Lorenza (case 3) | 12.5 | 5.60 | 0.7 | |
| Margaret | 11.9 | 5.72 | 0.6 | 9,400 |
| Liboria | 12.0 | 5.55 | 0.6 | 8,750 |

*Ectodermal lesions.* The nail changes occasioned by the moniliasis are not to be confused with the ectodermal changes which occur in rare instances of hypoparathyroidism. An interesting example of the latter condition was recently published by Emerson, Walsh and Howard together with a short discussion (9). Why these ectodermal changes occur in some cases of hypoparathyroidism and not in others is entirely unknown. They differ from the changes resulting from the moniliasis in that the skin and hair are involved as well as the nails, by the fact that all of the nails are involved (not only the fingernails as in case 1) and by the fact that the lesions clear up with specific therapy for the hypoparathyroidism. That these ectodermal changes are a result of the hypoparathyroidism is shown not only by the fact that they clear up with specific therapy but by their occurrence in cases of post-operative hypoparathyroidism (10). It is quite clear that case 3 had these ectodermal changes in addition to what was probably moniliasis; thus, besides the mouth and nail changes, she had alopecia of the scalp and of the eyebrows and marked hyperkeratosis of the skin. In this connection it should be noted that the toenails of case 1 were somewhat hypoplastic, and that both case 1 and case 2 had slightly hyperkeratotic skin.

Emerson, *et al.*, found a decreased cystine content of the nail parings in their case. This seems to be an important lead, and further studies in this direction should be made on cases of hypoparathyroidism and hyperparathyroidism to determine whether sub-clinical changes have occurred.

*True hypoparathyroidism, not 'pseudo-hypoparathyroidism.'* Pseudo-hypoparathyroidism (11) is a distinct disease entity which has the same serum calcium and phosphorus findings as are present in true hypoparathyroidism; however, the difficulty is not a lack of hormone but a failure on the part of the organism to respond to the hormone. This lack of response is best brought out by performing an Ellsworth-Howard test (12) which makes use of the most fundamental metabolic response to the hormone, namely the increased excretion of phosphorus in the urine. The patient is fasted; the urine is collected each hour for 3 hours before the intravenous administration of parathyroid hormone and then for 2 hours following the administration; the 5 urine samples are analyzed for the phosphorus content. In table 2 it will

TABLE 2. ELLSWORTH-HOWARD TEST ON *case 1*. NOTE MARKED INCREASED PHOSPHORUS EXCRETION WITH LOWERING OF SERUM PHOSPHORUS VALUE FOLLOWING PARATHYROID EXTRACT ADMINISTRATION

| Time[1] | Urine | | Serum | | |
|---|---|---|---|---|---|
| | Vol. | P | Ca | P | Alk. Phosphatase[2] |
| *hr.* | *cc.* | *mg.* | *mg./%* | *mg./%* | |
| 8–9 | 210 | 21 | 5.9 | 9.8 | 11.4 |
| 9–10 | 330 | 24 | | | |
| 10–11 | 180 | 21 | | | |
| *2 cc. parathyroid extract I.V.* | | | | | |
| 11–1 | 160 | 160 | | | |
| 1–2 | 231 | 231 | 5.7 | 7.2 | 15.6 |

[1] Urine collection, 8 A.M. to 2 P.M.
[2] Bodansky units.

be seen that the patient in case 1 showed a marked excretion of phosphate in response to the parathyroid hormone administration, an indication that his symptomatology was the result of lack of hormone rather than of failure to respond to the hormone.

*Certain errors in diagnosis of hypoparathyroidism.* The authors would like to emphasize certain points in the diagnosis of hypoparathy-

roidism, especially since they themselves were inexcusably slow at arriving at the correct diagnosis in case 1. Even if there is no history of carpopedal spasms, a case of idiopathic epilepsy should always be reviewed from the point of view of hypoparathyroidism. There have been 3 cases recently at the Massachusetts General Hospital all of whom had been diagnosed as idiopathic epilepsy for a period of years before the correct diagnosis of hypoparathyroidism was made.

That choked disks may be present in hypoparathyroidism is no new finding but nonetheless a very important thing to remember. This observation has been recently emphasized by Barr, MacBryde and Sanders (13).

## SUMMARY AND CONCLUSIONS

Three cases of idiopathic hypoparathyroidism in siblings are reported. Two and probably all three of these cases suffered from widespread chronic monilia infection; two additional cases in which idiopathic hypoparathyroidism was associated with moniliasis are reported; finally, attention is called to two siblings reported from the Children's Medical Service (5) in both of whom moniliasis was associated with Addison's disease and in one of whom hypoparathyroidism was also present.

The association of moniliasis with hypoparathyroidism is discussed from four points of view: *a*) no connection between the two conditions, *b*) hypoparathyroidism as a result of the moniliasis, *c*) moniliasis as a result of the hypoparathyroidism, and *d*) both conditions as a result of a third factor. No definite conclusion is reached, but it is pointed out that the time relationships in the case histories suggest that the moniliasis precedes the hypoparathyroidism.

Since the father and mother of patients 1, 2 and 3 were first cousins, and since all three patients, the father, and other siblings had congenital hypochromic polycythemia, the possibility exists that the susceptibilities to monilia infection and to hypoparathyroidism are both connected with some defect in the germ plasm.

The nail changes resulting from moniliasis did not improve in case 1 when the serum calcium was restored to normal by dihydrotachysterol therapy; they are, therefore, not to be confused with the nail changes which are part of a generalized ectodermal disorder which accompanies certain cases of hypoparathyroidism and which are relieved by specific therapy. Furthermore, the fact that the changes were confined to the fingernails and did not involve the toenails suggests an infectious as opposed to a metabolic etiology.

With the Ellsworth-Howard test it was demonstrated that case 1 reacted normally to parathyroid extract; this rules out 'pseudo-hypoparathyroidism.'

Attention is called to the previously reported association of papilledema and increased intracranial pressure with hypoparathyroidism; their combination in case 1 with Jacksonian epilepsy led to the faulty diagnosis of brain tumor.

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# Parathyroid Tetany Treated with Massive Doses of Vitamin D

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An earlier report (1) indicated the success attendant upon replacement of dosages of dihydrotachysterol varying from 0.25 to 0.75 cc. (of Hytakerol solution) with 50,000 to 200,000 U.S.P. units of vitamin D in four cases of parathyroid tetany. Systematic observations have been continued on two of these patients, and on four more, making a group of six who have been studied. Four of these have been on such therapy for two or more years, the other two for one and one-half years and for seven months, respectively. Certain of the details involved are here reported as evidence for the dependability and safety of this type of treatment.

The general plan has been to relax dietary restrictions previously considered necessary, thereby allowing the patient to use as much meat, egg and milk as desired in spite of the higher phosphorus intake involved. Calcium intake has always been fortified, usually by the 25 per cent solution of calcium chloride in sirup of glycyrrhiza previously described (1). Rarely patients have objected, preferring to use calcium lactate tablets, dissolved prior to ingestion. The added calcium intake has been 3 gm. of calcium chloride per day. The doses of vitamin D have been adjusted with the goal of freedom from any signs or symptoms of tetany, but not with any predetermined level of serum calcium or phosphorus in mind. The symptom which seems to be the most sensitive indicator of returning tetany is tingling in the arms and hands, less commonly a tightness in the larynx. Frank convulsive seizures, definite cramps in muscles, or positive Chvostek or Trousseau signs have never occurred when control was near a satisfactory state.

The dosage of vitamin D has been kept at what appeared a minimum for complete control under the above conditions. This was urged upon the patients for reasons of economy of material, and was accomplished by examinations in the out-patient clinic at intervals of not over a few months. Advantage was taken of these returns to the clinic, or occasionally into the hospital, to determine the serum calcium and phosphorus levels, and to look for any evidences of toxicity from the large doses of vitamin D employed. Standard urine examination, occasional determination of urea clearance, blood counts, and on a few occasions, roentgen-ray films of the renal regions were requested for this purpose. In none of these patients have we found even a suggestion of renal disturbance which could be attributed to the use of the vitamin.

There has been no evidence that an increasing dose of vitamin was required by any of our patients during the time of study. An apparent exception was associated with pregnancy in one of the two cases longest under observation. The increase from 200,000 to 300,000 units daily became advisable due to return of paresthesias, and was not preceded by a fall in serum calcium level. The increased dosage may not have been entirely necessary, but it has not been followed by a hypercalcemia. The daily vitamin D requirements of the members of the group are 150,000 units (2 patients),

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200,000 units (2 patients), 300,000 and 400,000 units (1 each). The pre-treatment levels were as follows: serum calcium 4.5 to 8.0 mg., average 6.9 mg., serum phosphorus 4.0 to 7.0 mg., average 5.9 mg. The serum calcium levels maintained at the time of most recent examination ranged from 8.3 to 10.5 mg., average 9.4 mg., inorganic phosphorus from 3.0 to 5.3 mg. per 100 cc., average 4.1 mg. There was no uniform tendency for lower phosphorus levels to occur with higher calcium values.

The graphic recording of serum calcium and phosphorus values throughout the course of these studies suggests that, at the time when intensive therapy is begun with either dihydrotachysterol or with vitamin D, a high serum phosphorus tends to fall during the period when serum calcium is rising. This is not seen in every case. Also when the serum calcium dropped due to inadequate therapy there was no uniform tendency for serum phosphorus to rise. This observation may be significant in the light of the recent reversal of opinion of Albright (2), who admits that the parathyroid hormone does not necessarily affect the serum calcium level by facilitating the excretion of phosphorus, although admittedly both the hormone and vitamin D are effective in causing increased renal excretion of phosphorus. Both hormone and vitamin apparently have other and more direct effects leading to an increased serum calcium level. We therefore find the serum phosphorus level far less helpful in estimating the need for revision of dosage than the serum calcium and the symptoms. We prefer to use the occurrence of the slightest symptoms as the sign for increased vitamin D dosage, and the rise of serum calcium above the minimum normal level of 10.5 mg. as a signal for reduction of the dose.

Attempts to use the Sulkowitch reagent (3) as a guide for upper limits of therapy have been disappointing in our hands. This seemed to be associated with a lower threshold for calcium than suggested by the authors of the test, and as a consequence symptoms were not always abolished when the excretion of calcium was demonstrable by this reagent. We insist that the patients who are using any type of treatment for control of tetany must have the serum calcium checked every few months. We have not seen rapid and large changes in this level except as expected from shifting the dosage of vitamin D. The maximum serum calcium level recorded in this series was 15.1 mg., with which there were no evidences of serious disturbance. The other high levels were 11.8, 11.8, and 12.5 mg. in patients who were at the time free from tetanic symptoms. It is therefore evident that whereas vitamin D can elevate serum calcium, the use of these dosages, seemingly very large, does not produce dangerous hypercalcemia in tetanic patients if simple precautions are employed to determine the trend of serum calcium levels. We have no data on the effect of similar doses in other than tetanic patients.

The vitamin D preparations employed in our study include Deltalin (Lilly), Drisdol in oil (Winthrop), Ostoforte (Frosst), Vitamin D (Squibb), each in gelatin capsules containing 50,000 U.S.P. units, and activated ergosterol in oil (Mead Johnson) in capsules of 50,000 and of 100,000 units. For the generous contributions of these supplies we and our patients are indebted to these firms. In several cases we have deliberately shifted from one brand to another, without any apparent shift in clinical response. With recent price quotations on these products it appears that the therapy of tetany can now be carried out at lower cost using the concentrated preparations of vitamin D than with clinically comparable amounts of dihydrotachysterol.

## CASE REPORTS

*Case 1. V. T. R.* (No. 209579) was treated for postthyroidectomy tetany over a total period of 4 years, using in turn Hytakerol, Ertron as previously reported (1), Mead Johnson's activated ergosterol, Ostoforte. She has required 150,000 to 200,000 units daily until the pregnancy, which has been normal, has recently terminated successfully. She has had calcium chloride supplements to her diet throughout the study.

*Case 2. D. E.* (No. 96338) was one of idiopathic tetany which began at age 5, possibly earlier, diagnosed first at age 21 and has been treated during the past 6.5 years, using Hytakerol, activated ergosterol as previously reported (1), and Drisdol (Winthrop). She has required 150,000 to 200,000 units daily. In addition to the continued oral infection with monilia this woman has had chronic sinusitis and recurrent periods of hypochromic anemia. There has been much gastro-intestinal instability. She prefers the use of

calcium lactate or gluconate to the chloride.

*Case 3. L. P.* (No. 201693) developed tetany several months after thyroidectomy at age 23, and has been under treatment for 6.5 years. After 4 years' use of Hytakerol she has used Mead-Johnson's activated ergosterol, Squibb's vitamin D, and Drisdol (Winthrop). Required doses have been from 50,000 to 200,000 units daily. The larger amounts have been required since it was considered wise to interrupt a pregnancy at the end of the first trimester, with development of a slowly healing abscess in the abdominal wall. The period of several months since the infection has subsided entirely has not been marked by any evidence of vitamin D over-dosage on the 200,000 unit level.

*Case 4. V. B.* (No. 82269) had her thyroid removed at age 34, immediately after which tetany appeared. Treatment was grossly inadequate after discharge until she returned to the hospital three years later, when therapy with Hytakerol was started, with good results; but treatment was not sustained during the next 6 years at home. On her third hospitalization, at age 43, she had the classical signs of tetany, including cataracts, and she was also psychotic. Treatment was begun with 400,000 units of Mead Johnson's activated ergosterol daily, and calcium chloride, which relieved all symptoms, eliminated the psychosis, and brought the serum calcium from 6 to 10 mg. in the course of 4 months. She has continued to respond similarly to Drisdol (Winthrop) and vitamin D (Squibb).

*Case 5. M. K.* (No. 225687) exhibited tetanic symptoms shortly after her thyroidectomy at age 59. Control was obtained by use of Hytakerol and calcium salts, but the dosage of 4 cc. daily was still causing a rise of serum calcium from the initial level of 4.5 to 9.0 mg. when therapy was changed to vitamin D. The dose of 100,000 units of activated ergosterol (Mead Johnson) was found inadequate, but 150,000 units daily has kept the patient free from paresthesias, although serum calcium has decreased from 10.0 to 8.2 mg. over the course of 8 months.

*Case 6. G. E.* (No. 200622) underwent partial thyroidectomies on three occasions between the ages of 30 and 34 years. After the third operation she developed tetany and was treated with Hytakerol. Use of activated ergosterol (Mead Johnson) requires 150,000 units daily, and gives satisfactory control of the tetany. This patient had long suffered from paroxysms of tachycardia with much discomfort and some hypertension. These phenomena led some of the clinical consultants to suspect recurrent thyrotoxicosis. Since the tetany has remained controlled the cardiac symptoms and hypertension have ceased to be significant. Ostoforte (Frosst) and Vitamin D (Squibb) have been similarly effective.

## SUMMARY

Six women with permanent and severe hypoparathyroid tetany have been maintained under complete symptomatic control by vitamin D and calcium salts orally. The duration of the treatment has been two years or longer in 4 cases. One patient has undergone an uncomplicated pregnancy. The doses varied from 150,000 to 400,000 U.S.P. units daily, and there have been no evidences of toxicity such as hypercalcemia or renal disturbances. The diets have been unrestricted in meat, egg and milk intake. When controlled by serum calcium determinations the management of tetany by vitamin D in large doses is apparently as safe as by dihydrotachysterol, and probably less expensive.

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# Combined versus Independent Hydrolysis and Extraction of Urinary 17-Ketosteroids

## With Special Reference to the Choice of Solvents[1]

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Among salient of the numerous unsolved ketosteroid problems are those concerned with the extraction from the urine of the estrogenic and androgenic substances which are excreted as products of the metabolism of various precursor hormones, many of which have not yet been identified. A similar situation exists for the neutral 17-ketosteroids, some of which are of the androgenic variety, while others are biologically inactive. The androgenic 17-ketosteroids are derived from the adrenal cortex and the testes; and there is evidence from Hill's transplantation experiments (1, 2) and Friedgood's observations on the post-oöphorectomy excretion of 17-ketosteroids (3) that the ovaries also contribute to the fraction. Furthermore, it is possible that a substance which is a non-androgenic corticosteroid at the time of its secretion may become an androgenic 17-ketosteroid by virtue of the transformation or degradation to which it is subjected during its metabolism and subsequent excretion. Some of the non-androgenic urinary ketosteroids are the end result of male sex hormone metabolism, while others probably stem from the corticosteroids. Since the ketosteroids are not secreted in the form in which they are excreted, the presumption is that they are present in the circulating blood for only a brief period of time. The earliest investigators of the urinary 17-ketosteroids were content to employ such methods for their hydrolysis and extraction as were then in use for the recovery of androgenic substances. Their efforts were directed principally toward the study and improvement of the Zimmermann colorimetric method of assay for the 17-ketosteroids. More recently, however, attention has been centered on the complicated problems concerned with the hydrolysis and extraction of the 17-ketosteroids. No matter to what point one may perfect quantitative assay methods, the final results must depend primarily on the essentially complete extraction of these 17-ketosteroids from the urine. The experiments reported in the present communication were made because of two statements which have come to be more or less generally accepted on the basis of widespread publication and constant repetition, although there is no adequate evidence to support them. The first of these is that simultaneous hydrolysis and extraction is superior to independent hydrolysis and extraction in the preparation of the urinary 17-ketosteroids for colorimetric assay. This attitude is reflected clearly in a recent paper by Venning, Hoffman and Browne (4, 5) who favored simultaneous hydrolysis and extraction for their experiments because "This procedure has been considered to be the one least likely to cause alteration in the original steroid." The second belief to which we have reference has been voiced by Hershberg and Wolfe (6) who stated that carbon tetrachloride "is regarded by Callow, Callow, Em-

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mons and Stroud (7) as being superior to benzene as a solvent for the extraction of steroids." This has resulted in the ever-increasing use of carbon tetrachloride as an extractive agent for the 17-ketosteroids.

It is of practical importance as well as historical interest to trace the course of events which led to the present situation. It is well recognized that the extraction of the urinary steroids is attended by a number of special chemical problems. The estrogens and androgens (including the biologically inactive 17-ketosteroids) are excreted in the urine in combination with other substances. These conjugated forms are water soluble and with the exception of certain estrogens, are low or completely lacking in biological activity in contrast to the corresponding uncombined steroids which are comparatively insoluble in water and have a substantial bioassay value which is characteristic for each of the known substances. Estriol and pregnanediol have been isolated as glucuronides from the urine of pregnant women; and estrone sulfate has been identified in the urine of pregnant mares (8, 9, 10). The conjugated 17-ketosteroids (androgens) which have been identified chemically are sodium androsterone sulfate which was isolated from the urine of a man suffering from an interstitial cell tumor of the testis with widespread metastases (4, 5) and sodium dehydroisoandrosterone sulfate which has been recovered from the urine of a normal man (11). Insofar as their estimation is concerned, a three-fold importance may be attached to the conjugated forms in which ketosteroids are excreted: *a*) the conjugated steroids must be hydrolyzed before they can be assayed chemically or biologically; *b*) hydrolysis apparently transforms or destroys a significant proportion of the original steroid content of the urine; and *c*) hydrolysis does not have the same effect on both conjugated and unconjugated steroids.

It is well known that biological or chemical assay of excreted conjugated steroids is impossible at present unless they are first freed from such combinations by hydrolysis. In 1934 and 1935, Zondek (12, 13), Smith and Smith (14) and Cohen and Marrian (15) reported this phenomenon for the estrogenic substances. That the same situation is applicable to the excreted androgens was first suggested in 1929 by the work of Funk, Harrow and Lejwa (16) who reported that extraction of highly acidified male urine gives a better yield of comb growth-promoting hormone than extraction of neutral urine. Later, in 1934, Adler (17) demonstrated the point even more conclusively by showing that a butanol extract of human male urine was biologically inactive until it was heated with trichloracetic acid subsequent to extraction. Gallagher, Koch and Dorfman (18) failed at first to recognize the essential rôle of hydrolysis as applied to the extraction of androgens, although they adopted the use of a 2-hour hydrolysis period as part of their routine method in order to study the estrogen excretion simultaneously. In 1937, however, Peterson, Gallagher and Koch (19) and Dingmanse, Borchardt and Laqueur (20) independently confirmed and extended Adler's previous observations on the recovery of androgens from urine.

Although hydrolysis is an essential procedure in the preliminary preparation of excreted steroids for their bioassay and chemical assay, there is no unanimity of opinion (21) as to the most desirable form in which to employ it. It is clear, however, unless some other way is found to accomplish the same purpose, that the least drastic form of hydrolysis compatible with the completeness of this procedure must be the immediate goal, since even relatively mild treatment with acid results in substantial destruction and chemical transformation of these substances. With reference to the androgens, with which the present report is principally concerned, Butenandt, Dannenbaum, *et al.*, (22) were the first to call attention to the formation of a chloro-derivative of dehydroisoandrosterone (3-chloro-$\Delta^5$-androstenone-17) as a result of the action of hydrochloric acid; and Wolfe, Fieser and Friedgood (23) found that approximately one-third of the dehydroisoandrosterone content of the urine from a patient with adrenocortical tumor was converted to this chloro-compound during a 10-minute hydrolysis with 15 volumes per cent of hydrochloric acid. Wolfe, Fieser and Friedgood (23) also demonstrated a number of other chemical artefacts which resulted from the hydrolysis of the ketosteroids in this urine,includ-

ing $\Delta^{3,5}$ androstadienone-17 and 3$\alpha$-hydroxyandrostenone-17. Pincus and Pearlman (24) likewise presented evidence on the conversion of androsterone and dehydroisoandrosterone to non-alcoholic substances by acid hydrolysis. Evidence that acid hydrolysis affects pure conjugates is contained in the work of Venning, Hoffman and Browne (4) who showed that hydrolysis of sodium androsterone sulfate results in variable proportions of androsterone and androstenone-17, and that synthetic sodium dehydroisoandrosterone sulphate yields equal quantities of dehydroisoandrosterone and 3-chloro-$\Delta^5$-androstenone-17 under similar conditions. The amount of actual destruction of the urinary steroids varies, of course, with the intensity of hydrolysis (degree of acidity and duration of treatment). Venning, Hoffman and Browne (4, 5) recovered 80 per cent of the free 17-ketosteroids after hydrolysis of crude fractions of the conjugate sodium androsterone sulfate, although only about 50 per cent of the known 17-ketosteroid content was recovered after hydrolysis of chemically pure sodium androsterone sulfate. They postulate that the relatively high yields after hydrolysis of the crude fraction are made possible by compounds in the urine which act in some way to prevent destruction of the 17-ketosteroids. These chemical studies of the destructive action of acid on steroids have been paralleled by investigations of the androgenic activity of urinary extracts subjected to similar treatment. It has been found that the bioassay value in such circumstances is likewise significantly affected (Butenandt, Dannenbaum, *et al.*, 22; Borchardt, Dingmanse and Laqueur, 25; Peterson, Gallagher and Koch, 19. Dingmanse and Laqueur (26) have also demonstrated that the $\beta$-fraction suffers a greater loss than the $\alpha$-fraction during hydrolysis.

Siebke (27) was among the first to employ simultaneous hydrolysis and benzene extraction. This method was subsequently adopted by Kemp and Pedersen-Bjergaard (28) and Borchardt, Dingmanse and Laqueur (25). In 1940 Talbot, Butler, MacLachlan and Jones (29) used simultaneous hydrolysis and carbon tetrachloride extraction in order to avoid the deleterious effects of hydrolysis. The results of a limited numbers of experiments reported by Callow, Callow, Emmons and Stroud (7) indicate that insofar as the assay of the total 17-ketosteroids is concerned, there is little choice between independent hydrolysis with subsequent benzene extraction and simultaneous hydrolysis and $CCl_4$ extraction. They recommend the former for use with large amounts of pooled urine and the latter for single specimens. Contrary to these final conclusions, they remarked at one point in their paper, that $CCl_4$ seemed to be a more efficient solvent than benzene for the 17-ketosteroids and androgens in one of their experiments. Reference to their data discloses that the differences to which they refer could not possibly have any statistical significance. Their remark, however, led Hershberg and Wolfe (6) to adopt $CCl_4$ as the solvent for use in their extractor, and Talbot, *et al.* (29), substituted $CCl_4$ for benzene for a similar reason.

The chemical behavior of conjugated and unconjugated steroids undergoing acid hydrolysis is not identical, and consequently the results of experiments with the former cannot be applied to the latter. Venning, Hoffman and Browne (4, 5) have demonstrated that mild acid hydrolysis combined with $CCl_4$ extraction causes serious damage to pure sodium androsterone and dehydroisoandrosterone sulfate, whereas Talbot, Butler, MacLachlan and Jones (29) found that unconjugated androsterone and dehydroisoandrosterone were unaltered by identical chemical treatment These observations indicate that simultaneous hydrolysis and extract on does not obviate the damaging effects of hydrolysis which have been ascribed heretofore to independent hydrolysis and extraction; and confidence in the efficiency of $CCl_4$ as the best extractive available for the urinary steroids was shaken by the observation that the method used by Hershberg and Wolfe (6) and Talbot (29) for the extraction of androgens and 17-ketosteroids was singularly inefficient for the extraction of estrogens as compared with ether-toluol (32) or benzene (table 1). A 42 to 86 per cent loss of the various estrogenic substances was detected after extraction by their $CCl_4$ method as compared with the results of assay on identical aliquots handled with the benzene method of Smith and Smith (14). This finding has a special bearing

on one of the clinical aspects of the steroid problem, inasmuch as it is often essential to determine the estrogenic and 17-ketosteroid content of a single 24-hour or 48-hour specimen of urine. Experiments concerned with this phase of the problem are being reported in a forthcoming communication.

The purposes of the present experiments are *a*) to compare the results of simultaneous hydrolysis and $CCl_4$ extraction insofar as the total urinary 17-ketosteroid excretion is concerned; and *b*) to investigate the desirability of using $CCl_4$ as an extractive for any of the urinary steroids.

TABLE 1. COMPARISON OF CARBON TETRACHLORIDE WITH BENZENE (CONTINUOUS EXTRACTION) AS A SOLVENT FOR ESTROGENS. URINE SPECIMEN, 24-HR. VOLUME FROM 38 WEEKS' PREGNANT WOMAN

| Method of Processing Aliquots of Urine Specimen | Estrogens Recovered—per 24-hr. Volume | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Estradiol | | Estrone | | Estriol | | Total | |
| | R.U. | μg. | R.U. | μg. | R.U. | μg. | R.U. | μg. |
| A. Smith & Smith hydrolysis and continuous 24-hr. benzene extraction (14) | | | | | | | 27,000 | |
| B. Smith & Smith hydrolysis and 2-hr. continuous $CCl_4$ extraction | | | | | | | 10,000 | |
| C. Simultaneous hydrolysis (15% HCl at 70° C.) and continuous 6-hr. $CCl_4$ extraction (6) | | | | | | | 5,330 | |
| D. Smith & Smith hydrolysis and Smith, Smith and Schiller extraction and separation (30) | 4,000 | 200 | 2,700 | 1,350 | 20,000 | 10,000 | 26,700 | 11,550 |
| E. Same as in D but re-extracted acidified NaOH (both strong and weak phenolic) by 2-hr. continuous $CCl_4$ instead of 24-hr. continuous benzene | 2,300 | 115 | 1,000 | 500 | 2,700 | 1,350 | 6,000 | 1,965 |
| Loss as compared with (D) | | 42% | | 64% | | 86% | | 83% |

From these results one may conclude that continuous $CCl_4$ extraction is not a suitable method for the recovery of urinary estrogens. The indications are that prolonging the time of extraction would give less rather than more recovery (compare B and C above). This may be due to the fact that water is soluble in $CCl_4$. The boiling $CCl_4$ thus becomes strongly acid and more estrogen destruction is induced during extraction. The longer the extraction period (as in simultaneous hydrolysis and extraction), the greater is the destruction. Water is not soluble in benzene, which is neutral at the end of a 24-hour continuous extraction of urine and 15% HCl. Heating in an acid solution destroys estrogens quite rapidly (14).

We are indebted to Dr. O. Watkins Smith of the Fearing Research Laboratory for the results of these experiments.

## METHODS AND MATERIALS

In view of the observations of Callow, *et al.*, (5), it appears that $CCl_4$ differs little in efficiency from benzene as a solvent for the 17-ketosteroids when used according to their technic. Consequently it was considered more expedient to compare the efficiency of other solvents with $CCl_4$ rather than to reinvestigate the relative merits in the use of benzene. Of these solvents which were considered for these experiments, ether and toluol seemed the most suitable from various theoretical and practical viewpoints. Accordingly the results of ether-toluol extraction of identical aliquots of urine were compared with those of two types of $CCl_4$ extraction, *viz.*, simultaneous and independent hydrolysis and extraction. The ether-toluol extraction was made essentially in accordance with the Smith and Smith modification of the Cohen and Marrian technic (30), a method which has also been employed by Pincus and Pearlman (24). Sixty-eight 24-hour or 48-hour specimens of urine were collected from 32 subjects, some of whom were normal young adult males and females, while others were classified among one of a number of classical endocrinopathies (Addison's disease; myxedema; hypogonadism). These urines were hydrolyzed, extracted and prepared for assay in accordance with either two or all three of the methods which are outlined in detail forthwith. The urines were divided into two or three equal aliquot portions depending on the number of

experiments to be made with them.

*Method A* consisted of the standard procedure of independent hydrolysis and $CCl_4$ extraction originally practised by Hershberg and Wolfe (6) and subsequently adopted by Talbot, *et al.*, (29). One liter of a 24-hour or 48-hour specimen of urine or an aliquot made up of one liter was acidified with 150 cc. (15 volumes per cent) concentrated C.P. hydrochloric acid and the mixture quickly brought to a boil and kept there for 10 minutes under a reflux condensor. The mixture was then cooled immediately under running tap water to 50 to 60° C. and introduced into a Hershberg-Wolfe apparatus properly charged with $CCl_4$. Extraction was permitted to proceed for two hours in most instances. Contrary to the report of Hershberg and Wolfe (6) and Tablot, *et al* (29), we found that the bulk of the 17-ketosteroid fraction was not extracted within one-half or even one hour. Re-extraction with ether or residual urines from such a one-hour extraction yielded significant quantities of the 17-ketosteroid material. The estrogenic and other ketonic substances were removed from the $CCl_4$ extract by washing in a separatory funnel with three 50-cc. portions of 1 N NaOH and three 25-cc. portions of 1 N NaOH. The $CCl_4$ was then evaporated over a hot water bath under reduced pressure and the dry residue was taken up in absolute alcohol for colorimetric assay as given in a previous communication (30). A color correction was applied in order to compensate for the non-specific chromogen content of the extracts (32).

*Method B* was used parallel with method A on an identical aliquot of urine, and differed from it only in that the hydrolysis was conducted simultaneously with, instead of independently of, the extraction. One liter of a 24-hour or 48-hour urine, or an aliquot made up to one liter, was acidified with 150 cc. (15 per cent) of concentrated C.P. HCl and simultaneously hydrolyzed and extracted with $CCl_4$ for 6 hours in the Hershberg-Wolfe apparatus. In accordance with Talbot's technic, the body of the extractor was insulated by an asbestos jacket in order to keep the mixture of urine, acid and $CCl_4$ just below the boi'ing point of the latter. The remaining steps in this procedure were identical with those described for method A.

*Method C* consisted of the Smith and Smith modification of the Cohen and Marrian technic for the extraction of estrogens from urine (30). An aliquot of urine, identical with those used in the two previous experiments, was hydrolyzed by boiling under a reflux condenser for 10 minutes with 150 cc. (15 volumes per cent) of concentrated C.P. HCl, and then cooled immediately under running tap water. The specimen was then shaken in a separatory funnel on four successive occasions with a quantity of ether equal to one-fifth the volume of the specimen. The residual urine was discarded. The emulsion formed in the ether extract was then removed and the acidic and phenolic impurities extracted by shaking with 25-cc. portions of a saturated solution of sodium carbonate. The ether solution was then rinsed with three washings of 25 to 30 cc. of distilled water. The remaining neutral ether extract was evaporated to a residue over a hot water bath, and the residue was quantitatively rinsed into a separatory funnel with four 25 cc. portions of toluene. The toluene solution was then shaken with four 30-cc. portions of 1 N NaOH and washed with three 25-cc. portions of distilled water. The NaOH fractions, preserved for estrogen assay, were extracted with benzene in the Smith and Smith continuous extractor and treated subsequently in the manner outlined by them for the separation of estrone, estriol and estradiol (30). The toluol fraction was evaporated to a residue over a hot water bath under reduced pressure, dissolved in absolute alcohol and prepared for colorimettric assay in accordance with the technic described above.

In order to interpret more adequately the results obtained with methods A, B and C, it was essential to perform certain additional procedures, among which were the following: *a*) The extracts prepared by methods A and C were treated with Girard's reagent and then assayed with the Zimmermann reaction. Total absorption spectra were then made of the colors developed during this reaction. It was possible thus to compare both qualitatively and quantitatively the chromogen content of

the extracts prepared by method A and C.

*b*) The 17-ketosteroid content of extracts prepared by methods A and C were reassayed chemically with the $SbCl_3$ method, which measures androsterone and its isomers and androstenone-17 quantitatively (33). Since dehydroisoandrosterone constitutes such a small proportion of the excreted 17-ketosteroids, it is of little moment that the $SbCl_3$ method does not measure it to any extent. These considerations suggested that the $SbCl_3$ method would indicate for all practical purposes whether or not the higher values obtained with method C were due to chromogens derived specifically from 17-ketosteroids or from other non-specific sources.

*c*) The residual urines after initial treatment with method A (independent hydrolysis and $CCl_4$ extraction) were re-extracted with ether and toluol in accordance with method C in order to determine the completeness of extraction with method A.

*d*) The residual urines after initial treatment according to Method B (simultaneous hydrolysis and $CCl_4$ extraction) were re-extracted with ether and toluol in accordance with method C in order to determine the completeness of extraction with method B.

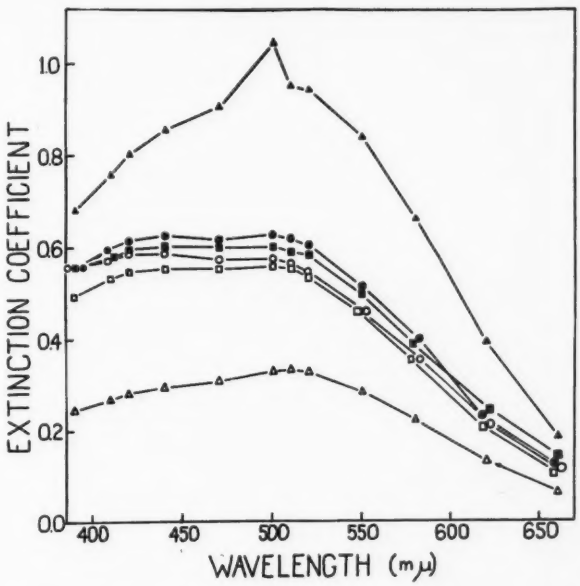


FIG. 1. Absorption spectra of crystalline and urinary 17-ketosteroids assayed colorimetrically by aqueous alcohol modification of the Zimmermann reaction.

| Symbol | Extracts and Androgens | Amounts | $\frac{500}{410}$ Ratio |
|---|---|---|---|
| ▲ | Dehydroisoandrosterone | 120 μg. | 1.38 |
| ● | $CCl_4$, Extract #3 | 0.1 cc. | 1.06 |
| ■ | Toluol, Extract #1 | 0.05 cc. | 1.03 |
| ○ | $CCl_4$, Extract #1 | 0.2 cc. | 1.00 |
| □ | Toluol, Extract #3 | 0.05 cc. | 1.05 |
| △ | Dehydroisoandrosterone | 40 μg. | 1.23 |

Procedures (*a*) and (*b*) were done through the courtesy of Dr. Gregory Pincus to whom we are indebted for these results.

## RESULTS

The absorption curves in procedure (*a*) were determined by an aqueous alcoholic modification of the Zimmermann reaction. Procedures (*a*) and (*b*) have established that similar chromogen-producing substances, which are

determined colorimetrically by the Zimmermann reaction, are extracted by methods A and C, and that these assayed chromogens represent the 17-ketosteroid content of the $CCl_4$ and ether-toluol extracts. Analysis of the absorption spectra of the extracts prepared by methods A and C shows that there are no significant qualitative differences between the results of the two methods of extraction, although the quantitative differences are quite apparent (fig. 1). Further study of these extracts by the $SbCl_3$ method of assay, which is specific for 17-ketosteroids, established the fact that the ether-toluol method of extraction removed more true 17-ketosteroids than the more efficient of the two $CCl_4$ methods (table 2).

method B (simultaneous hydrolysis and extraction). In 14 of these 21 specimens, method A gave results which were from 14 to 88 per cent (average of 40 per cent) greater than those obtained on identical aliquots by extraction according to method B. Both methods yielded essentially similar results (within 1 mg. of each other) in 6 instances; and only in one experiment were the results of assay after method A less than after method B (19 per cent).

Comparison of the 17-ketosteroid content of urinary extracts assayed by the Zimmermann reaction after extraction by methods A and C showed that the use of method C generally resulted in higher values than those obtained after treatment with method A (table 5). In 9 of the 19 identical aliquots of urine extracted

TABLE 2. 17-KETOSTEROID EXCRETION AS DETERMINED BY THE ZIMMERMANN AND $SbCl_3$ METHODS OF ASSAY EXPRESSED AS MG. EQ. OF ANDROSTERONE PER 24 HOURS

| Subject | No. of Specimen | Methods | | | | | |
|---|---|---|---|---|---|---|---|
| | | $B_z$ | $B_zG$ | $B_{sb}G$ | $C_z$ | $C_zG$ | $C_{sb}G$ |
| Normal young adult female | 1 | 9.5 | 6.7 | 6.2 | 22.9 | 20.8 | 16.4 |
| | 2 | 17.3 | 16.1 | 12.9 | 26.6 | 22.5 | 17.8 |
| | 3 | 18.8 | 15.0 | 11.6 | 25.0 | 21.2 | 17.5 |

$B_z$ = Extraction by method B; assay by Zimmermann reaction; $B_zG$ = Extraction by method B and subsequent treatment with Girard's reagent; assay by Zimmermann reaction. $B_{sb}G$ = Extraction by method B and subsequent treatment with Girard's reagent; assay by $SbCl_3$ method. $C_z$ = Extraction by method C; assay by Zimmermann reaction. $C_zG$ = Extraction method C and subsequent treatment with Girard's reagent; assay by Zimmermann reaction. $C_{sb}G$ = Extraction by method C and subsequent treatment with Girard's reagent; assay by $SbCl_3$ method.

The 17-ketosteroid content of urinary extracts prepared by method C (ether-toluol) was significantly greater than that obtained by method B (simultaneous hydrolysis and $CCl_4$ extraction). Thus, of 67 identical aliquot specimens extracted by both methods, 55 gave results which were from 14 to 140 per cent (average of 50 per cent) higher for method C than for method B. The results were essentially identical (difference of 1 mg. or less) in the remaining 12 specimens. In no instance did method B give results which were greater than those obtained with method C (table 3).

The 17-ketosteroid content of urinary extracts assayed by the Zimmermann reaction after extraction and purification by method A was likewise greater than that resulting from treatment by method B (table 4). A total of 21 specimens of urine was extracted with $CCl_4$ according to the procedures of method A (independent hydrolysis and extraction) and by these two methods, the results of assay after Method C were from 1 to 67 per cent (average of 29 per cent) higher than after treatment with method A. The results of assay were essentially identical (within 1 mg. of each other) in 7 of the 10 remaining specimens. In the other 3 specimens of this series, the results of assay after treatment with method A were an average of 13 per cent higher than after treatment with method C.

It may be noteworthy that of the 10 specimens in which method A yielded results which were equal to or slightly higher than those obtained with method C, 5 were from a single normal individual. Why all of the specimens from this apparently normal individual should have yielded results contrary to the general trend is unknown. The other 5 specimens were obtained from cases of Cushing's syndrome, primary amennorhea in a woman of 37, spontaneous myxedema, and anterior hypophyseal

deficiency with secondary involvement of thyroid and adrenals. It is possible that a portion of the ketosteroids excreted by these individuals differed from those ordinarily found as end-products of metabolism and that their solubilities may have been essentially identical in $CCl_4$ and ether-toluol.

TABLE 3. COMPARISON OF YIELDS OF 17-KETOSTEROIDS BY METHODS B AND C

| Subject | Diagnosis | Methods B>C | | Per cent Differences |
|---|---|---|---|---|
| | | *B* | *C* | |
| W | normal | 18.0 | 35.6 | 98 |
| | | 22.7 | 42.3 | 86 |
| | | 21.4 | 27.6 | 29 |
| | | 27.6 | 38.0 | 38 |
| | | 19.9 | 26.2 | 32 |
| | | 22.1 | 30.3 | 37 |
| | | 24.5 | 30.8 | 26 |
| | | 36.5 | 37.6 | 30 |
| Ta | normal | 14.7 | 15.8 | 1 |
| | | 12.1 | 16.4 | 36 |
| | | 10.6 | 16.2 | 53 |
| | | 13.1 | 18.4 | 40 |
| | | 6.9 | 8.9 | 29 |
| C | normal | 18.8 | 20.9 | 1 |
| | | 18.1 | 25.3 | 40 |
| | | 13.7 | 21.8 | 59 |
| | | 18.0 | 23.1 | 28 |
| | | 18.6 | 23.4 | 26 |
| | | 14.9 | 19.3 | 29 |
| | | 17.2 | 18.3 | 1 |
| P | normal | 9.5 | 22.9 | 141 |
| | | 17.3 | 26.6 | 54 |
| | | 18.8 | 25.0 | 33 |
| | | 10.7 | 22.5 | 110 |
| | | 11.3 | 20.8 | 84 |
| | | 13.8 | 22.6 | 64 |
| | | 17.1 | 21.9 | 28 |
| | | 13.0 | 21.0 | 61 |
| Fo (male) | normal | 8.2 | 19.9 | 143 |
| Fr (male) | normal | 16.5 | 20.9 | 29 |
| | | 15.2 | 17.0 | 12 |
| | | 15.4 | 17.5 | 14 |
| B | myxedema | 4.5 | 9.5 | 111 |
| M | myxedema | 3.8 | 6.9 | 82 |
| D | myxedema | 6.3 | 7.7 | 22 |
| S | myxedema | 8.6 | 11.4 | 33 |
| S | Addison's disease | 3.1 | 4.5 | 45 |
| W. H. | Addison's disease | 6.8 | 10.8 | 59 |
| P | virilism | 24.5 | 31.4 | 28 |
| J | virilism | 13.7 | 17.0 | 24 |
| O | virilism | 12.0 | 21.0 | 75 |
| F | hirsutism | 25.8 | 38.1 | 48 |
| Ge | Cushing's syndrome | 25.2 | 44.4 | 76 |
| Go | primary amenorrhea | 8.2 | 10.4 | 27 |
| Tr | chronic nephritis | 3.5 | 6.2 | 77 |
| D | acromegaly | 3.2 | 5.3 | 66 |
| B | cirrhosis | 5.8 | 7.0 | 21 |
| Wh | ovarian deficiency, pyelonephritis | 2.3 | 5.3 | 130 |
| We | Addison's disease | 2.4 | 4.5 | 88 |
| B | Addison's disease | 5.1 | 8.5 | 67 |
| H (male) | normal | 21.7 | 23.3 | 74 |
| E (male) | normal | 15.8 | 18.1 | 15 |
| B (male) | normal | 13.2 | 18.8 | 42 |
| P (male) | normal | 18.7 | 23.5 | 26 |
| M | Addison's disease | 2.5 | 6.0 | 140 |

TABLE 3. COMPARISON OF YIELDS OF 17-KETOSTEROIDS BY METHODS B AND C—*Continued*

| Subject | Diagnosis | Methods B=C | | Per cent Differences |
|---|---|---|---|---|
| | | *B* | *C* | |
| Ta | normal | 16.0 | 15.9 | |
| | | 14.7 | 15.7 | |
| | | 14.9 | 15.1 | |
| M | myxedema | 2.6 | 3.1 | |
| B (male) | hypogonadism | 4.1 | 4.7 | |
| L | anterior hypophyseal deficiency | 1.0 | 1.1 | |
| D | Addison's disease | 1.1 | 1.6 | |
| | | 1.8 | 1.8 | |
| J.H. | Addison's disease, diabetes mellitus | 2.4 | 2.6 | |
| G | Addison's disease, hypothyroidism | 0.4 | 1.0 | |
| M | Addison's disease | 0.5 | 0.9 | |
| Mc | myasthenia gravis | 1.7 | 2.7 | |

One may conclude from these experiments that the ether-toluol extraction of 17-ketosteroids is significantly more efficient and more uniformly dependable than that achieved by either of the two $CCl_4$ methods. Contrary to the belief of Talbot, *et al.*, (29), actual comparison of the results obtained by the two $CCl_4$ methods shows that independent hydrolysis and $CCl_4$ extraction is more efficient, so far

TABLE 4. COMPARISON OF 17-KETOSTEROID YIELDS BY METHODS A AND B

| Patient | Diagnosis | Methods A & B | | Per cent Differences |
|---|---|---|---|---|
| | | Methods A<B | | |
| Ta | normal | 19.4 | 13.1 | 48 |
| | | 19.8 | 14.7 | 35 |
| | | 17.0 | 14.9 | 14 |
| | | 9.7 | 6.9 | 41 |
| P | normal | 19.7 | 13.0 | 52 |
| | | 20.7 | 12.0 | 73 |
| M | myxedema | 5.6 | 3.8 | 47 |
| B | myxedema | 5.7 | 4.5 | 27 |
| F | hirsutism | 30.2 | 25.8 | 17 |
| O | virilism | 15.0 | 12.0 | 25 |
| P | virilism | 28.8 | 24.6 | 17 |
| C | hirsutism | 25.5 | 21.6 | 18 |
| G | Cushing's syndrome | 47.4 | 25.2 | 88 |
| Tr | Addison's disease | 5.6 | 3.5 | 60 |
| | | Methods A=B | | |
| Ta | normal | 16.3 | 16.0 | |
| S | myxedema | 9.5 | 8.6 | |
| D | myxedema | 5.9 | 6.3 | |
| L | anterior hypophyseal deficiency | 0.8 | 1.0 | |
| B (male) | hypogonadism | 4.7 | 4.1 | |
| | | Methods A>B | | |
| P | virilism | 11.1 | 13.7 | 23 |

as the total 17-ketosteroid assay is concerned, than simultaneous hydrolysis and $CCl_4$ extraction. Analysis of the data obtained with the ether-toluol method C indicates, furthermore, that curves of the 17-ketosteroid excretion of a single individual, studied over a period of several weeks are relatively smooth and lack the wide swings characteristic of those obtained after extraction with methods A and B. This finding further confirms our conclusion that extractions with method C are more uniform and dependable than those made by either of the two $CCl_4$ methods.

TABLE 5. COMPARISON OF 17-KETOSTEROID YIELDS BY METHODS A AND C

| Patient | Diagnosis | Methods A & C | | Per cent Differences |
|---|---|---|---|---|
| | | Methods A>C | | |
| P | normal | 19.7 | 21.0 | 1 |
| S | Addison's disease | 9.5 | 11.4 | 20 |
| M | myxedema | 5.6 | 6.9 | 23 |
| D | myxedema | 5.9 | 7.7 | 31 |
| B | myxedema | 5.7 | 9.5 | 67 |
| P | virilism | 28.8 | 31.4 | 1 |
| | | 11.1 | 17.0 | 53 |
| O | virilism | 15.0 | 21.0 | 40 |
| F | hirsutism | 30.2 | 38.1 | 26 |
| | | Methods A=C | | |
| Ta | normal | 16.3 | 15.9 | |
| | | 9.7 | 8.9 | |
| | | 19.4 | 18.4 | |
| G | primary amenorrhea | 12.0 | 11.1 | |
| L | anterior hypophyseal deficiency | 0.8 | 1.1 | |
| B (male) | hypogonadism | 4.7 | 4.7 | |
| Tr | Addison's disease | 5.6 | 6.2 | |
| | | Methods A<C | | |
| Ta | normal | 17.0 | 15.1 | 13 |
| | | 19.8 | 15.7 | 26 |
| G | Cushing's syndrome | 47.4 | 44.4 | 1 |

Procedures (*c*) and (*d*) were undertaken to determine why independent hydrolysis and $CCl_4$ extraction is more efficient than simultaneous hydrolysis and $CCl_4$ extraction for the removal of 17-ketosteroids from urine. The lower values obtained by simultaneous hydrolysis and extraction could not be attributed to an incomplete extraction since the amount of 17-ketosteroids recovered in the re-extraction with ether-toluol was insignificant except in those instances in which the original extraction with $CCl_4$ was limited to one hour. The lower values must have been due either to inadequate hydrolysis or to destruction of the 17-ketosteroids by heat and acid in the interval between hydrolysis and extraction. The latter would not be an unexpected finding since hydrolysis undoubtedly occurs at a more rapid rate than extraction. The still higher values for 17-ketosteroids obtained after ether-toluol extraction must be attributed to the superiority of ether-toluol over $CCl_4$ as an extractive agent for these steroids.

## DISCUSSION

Experiments in the ketosteroid field may be grouped for convenience of reference into three categories, *viz.*, those which are concerned with *a*) the chemical isolation of the various urinary 17-ketosteroids; *b*) the bioassay of the urinary androgens; and *c*) the colorimetric assay of the total 17-ketosteroid excretion. Each of these procedures will be affected differently by hydrolysis and extraction. The destruction of the 17-ketosteroids during hydrolysis would, of course, affect the results in each of the three types of investigation. Chemical transformation (production of chemical artefacts) would obviously interfere with isolation of the original steroids, and undoubtedly would alter the bioassay value of the urinary androgens. The chloro-derivative of dehydroisoandrosterone, for instance, is biologically inactive, and its formation thus interferes to some extent with the results of bioassay (dehydroisoandrosterone ordinarily accounts for only a small fraction of the total androgen content of a 24-hour urine sample, and has only one-third the activity of androsterone in the capon method of assay). For most clinical purposes, however, it makes no difference whether or not a large portion of dehydroisoandrosterone is converted to its chloro-derivative by hydrolysis prior to chemical assay since both compounds yield the same intensity of color per unit of weight in the absolute alcohol modification of the Zimmermann reaction (31). It is quite possible, furthermore, that this would hold true for other transformation products so that chemical assay of the total 17-ketosteroid fraction may not be affected to a significant extent by this undesirable aspect of hydrolytic action on urinary steroids. This factor probably explains why simultaneous hydrolysis and extraction

may result in higher bioassay values than those which are obtained with independent hydrolysis and extraction, whereas the latter method is more efficient so far as the chemical assay of the total 17-ketosteroids is concerned. The data suggest that relatively more destruction than transformation of the 17-ketosteroids takes place during combined hydrolysis and extraction, whereas the reverse is true of independent hydrolysis and extraction. In the former method, hydrolysis occurs more rapidly than extraction and the steroids are exposed for 6 hours to heat and acid; with the latter method, heat is applied during only a brief hydrolysis and the subsequent 2-hour extraction is cold.

## SUMMARY

Identical aliquots of urine in triplicate were subjected to independent hydrolysis and $CCl_4$ extraction, simultaneous hydrolysis and extraction, and ether-toluol extraction in accordance with the Smith and Smith modification of the Cohen and Marrian technic (originally devised for the separation of estrogens from urine). Colorimetric assay of the 17-ketosteroids was made by an absolute alcohol modification of the Zimmermann reaction. Independent hydrolysis and $CCl_4$ extraction resulted in a significantly higher yield of urinary 17-ketosteroids than that obtained by simultaneous hydrolysis and $CCl_4$ extraction. The ether-toluol extraction was found to be superior to either of the two $CCl_4$ methods. The $SbCl_3$ method of assay and total absorption spectra of the chromogens developed in the various urinary extracts as a result of the Zimmermann reaction indicated that true 17-ketosteroids were being determined in each instance.

Carbon tetrachloride is much inferior to either benzene or ether-toluol for the extraction of estrogens from urine.

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# Dysfunctional Uterine Bleeding[1]

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RICHARDSON (1) defines dysfunctional bleeding as that which appears in the absence of gross lesions, at unexpected times or in abnormal amounts. The cause is unknown. There are many theories. It is believed to be due to an imbalance of the ovarian and pituitary hormones. Dysfunctional uterine bleeding is extremely bothersome to the patient and to the physician. Therefore the problem is of considerable practical interest to the gynecologist, endocrinologist, internist, surgeon and the general practitioner.

The pathogenesis of the disorder has been somewhat clarified in recent years by the contributions from experimental laboratories. True pathological bleeding and menstrual bleeding have been produced experimentally with the use of natural and synthetic estrogenic hormones in women and monkeys (1–4).

Dysfunctional bleeding may occur from a resting, proliferative or hyperplastic type of endometrium, with or without dilated glands or from an atrophic type of mucosa. Kurzrok, (5) believes the responsible factors reside in the endometrium. Markee (6) and Bartelmez (7) believe that the spiral arterioles in the endometrium are important both in normal and abnormal uterine bleeding.

At one time, the theory of estrogen withdrawal was proposed as the basis of normal and abnormal menstruation, but this does not explain the bleeding that is clinically noted during the period of administration of large doses of estrogen. The cystic glandular and hyperplastic type of endometrium, which constitutes probably one-third of all endometrial types in functional bleeding, is not satisfactorily explained by an excess of the blood and urine estrogens. Kurzrok (5) pointed out that neither the blood nor the urine of such patients showed high estrogenic titers. The author has given large daily doses of diethylstilbestrol (25 to 100 mg. per day for 4 to 12 months) to 76 women in attempts to produce hyperestrogenic blood levels. In 72 women there was no excessive uterine bleeding of the type seen in cases of dysfunctional uterine bleeding; 4 developed excessive uterine bleeding, an incidence of 5.5 per cent. In this series 85 per cent of the specimens of endometrium were in the proliferative state, with or without dilated glands. Some cases had atrophic endometrium. The endometria were similar in appearance whether as little as 1.0 or as much as 100.0 mg. of stilbestrol was taken daily for periods of 6 months to 2 years. Furthermore, other tissues sensitive to estrogens seldom show the effects of overstimulation such as enlargement of the breast or uterus. Kurzrok (8) has expressed the opinion that functional uterine bleeding is an endometrial affair, the endometrium requiring more than its share of the estrogens and this in turn causing more estrogen to be produced by the ovary. Thus the endometrium may be the cause of the cystic follicles so frequently found in the ovaries of such patients rather than the cystic follicles producing the hyperplastic endometrium.

It is the view of McGinn (9) that all women, at one time or another, may experience some of these functional disturbances during active sex life. In many instances, it is but a temporary phase. If some palliative measures can be used the body will readjust its endocrine pattern and the cycle will again have a definite periodicity. Hamblen (10) says, "Normal women may have two to five anovulatory cycles in one year. Minor menstrual irregularities are often normal for the individual and only when undesired sterility is related to these irregu-

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[1] Permission to do this research granted by the Research Committee of the Jefferson Davis Hospital.

larities, or when there is a depleting hemorrhage, is therapy justified."

Most women have had in their lives at least one period of excessive and irregular uterine bleeding which corrected itself without treatment. A dilatation and curettage is sometimes needed but a more radical procedure such as a hysterectomy is not necessary for this one incident.

### ENDOCRINE THERAPY

The use of endocrine preparations such as testosterone, chorionic gonadotropin, equine gonadotropin and the combination of human chorionic gonadotropin with whole pituitary extract, and thyroid has not produced uniformly successful or desirable results.

*Testosterone.* Testosterone undoubtedly will check functional bleeding, as demonstrated by Mazer and Mazer (11), and by Salmon and his associates (12). The *modus operandi* probably is by its depressing effect on the pituitary gland and subsequent depression of ovarian activity. The cost has made its use impractical for some patients. More important is the possibility of embarrassing side effects such as the development of male characteristics, hirsutism, atrophy of the breasts and change of voice. Unhappily, not all of these side effects disappear with the cessation of treatment. In 28 cases the author has observed one case in which the endocrine balance has been permanently disturbed after testosterone was given.

The use of testosterone is advocated less frequently now than a few years ago, although it may be employed occasionally at the menopause in patients with large multiple myomas who are to be conditioned for an operation. Doses of 400 mg., or less, per month are generally sufficient.

*Pituitary gonadotropic substances.* The pituitary gonadotropic substances theoretically should constitute a satisfactory method of treatment, because they are supposed to exert trophic influences upon the ovary which, presumably, is not functioning properly. The writer has obtained negative results with this type of treatment in 21 cases of dysfunctional uterine bleeding.

*Human chorionic gonadotropin.* Human chorionic gonadotropin (which is known also as APL, pregnancy urine extract), has been found sadly lacking in effect in checking and clearing up functional bleeding (Geist, 13). Indeed it has been found wanting in most fields of gynecic endocrinology. It has even been known to produce ovarian damage by the formation of atretic follicles. Any beneficial effects, as reported by some, were said to be merely coincidental (14). The negative results may be due to a foreign protein reaction that is usually produced by the injections, as has been shown by Hamblen (15) and the author (16). Kurzrok (8) and the author each have used small blood transfusions in checking functional uterine bleeding. The donor used was a pregnant woman in her middle trimester. Kurzrok believes the value of the therapy was by reason of the high concentration of pregnancy gonadotropin at this period. It has been demonstrated that the cessation of the uterine bleeding was due to the high level of estrogen, and not to the gonadotropin (17).

In 55 cases the author has not been able to change the character of the menstrual cycle by giving doses of 10 to 50 cc. of human chorionic gonadotropin intramuscularly 2 to 3 times weekly, over a period of 1 to 6 weeks.

*Equine gonadotropin.* Equine gonadotropin (from pregnant mares' serum) has had more popularity than human chorionic gonadotropin, although in the writer's experience is has proven of little or no value. Equine gonadotropin is a potent principle, as evidenced by its causing ovulation in experimental animals. Ever since Davis and Koff (18) in 1938 and Sevringhaus in 1940 (19) claimed they could produce artificial ovulation in women by means of this hormone, it has been used in tremendous quantities. Equine gonadotropin has been used in many instances of ovarian failure such as sterility, menorrhagia and metrorrhagia, amenorrhea and even dysmenorrhea, and the reports of the results have been conflicting.

Evidence, now accumulating rapidly, shows that it is extremely doubtful whether equine gonadotropin induces ovulation or improves ovarian function. Geist (13) and his associates in a careful analysis of 91 cases, followed by observation at laparotomy, state they have never seen an ovulation result from its use. Novak and Hofbauer, in discussing Geist's

paper state it is of little or no value and should be discarded. The author gave large doses to 12 normal women and did not observe a change in the endometrial pattern or in the menstrual rhythm (17). The ovaries of these women were not observed. Sexton and Vogt (20) reported only meager results in its use for the treatment of menorrhagia. Erving and his associates (21) found 81 per cent of their cases unaffected by equine gonadotropin and in no case was there evidence of stimulation of ovulation. Recently Gray (22) in evaluating equine gonadotropin, found it to be of value in only 50 per cent of his cases of metrorrhagia, a figure easily duplicated by spontaneous cures. The use of pregnant mares' serum is not indicated in any condition that the author has seen in obstetrics and gynecology. Equine gonadotropin in my opinion, in its present form for human therapy will become one of the hormones in the passing parade.

*Combined gonadotropins.* Another gonadotropic preparation which at present appears to have promise is that of chorionic gonadotropin in combination with a whole pituitary extract and a pituitary synergist.[2] In a preliminary report, Mazer and Ravetz (23) state that with its use dysfunctional bleeding was arrested in 14 of 18 patients, and menstrual flow evoked in 19 of 23 severely amenorrheic women, some of whom had not menstruated for years, despite many other forms of treatment. By use of the same preparation the author has produced definite changes in the endometrial tissue, ovaries and menstrual cycle in 15 normal women. On the other hand Geist (13) has not found combined gonadotropins of much more value than the other pituitary and pituitary-like hormones. Although it is too early to determine the value of the drug in our sterility cases, it has not changed the anovulatory endometrial pattern to that of a normal secretory state, in our experience. However, of all the pituitary gonadotropic preparations, it appears to be the most promising. It should be remembered that other substances experienced a similar flurry of popularity.

*Thyroid.* In a discussion of functional uterine bleeding a word should be included on the use of thyroid. Thyroid substance is one of the most valuable of the endocrine substances. There is a tendency to use the newer, and more expensive endocrine products, in place of this simple and time-tested substance. Fresh desiccated thyroid in our experience has proven of value in all female endocrine cases save those produced by hyperthyroidism. We have used thyroid in dysfunctional uterine bleeding in conjunction with diethylstilbestrol and lipoiodine therapy. Of course, its value in a true hypothyroid case is unquestioned. Its use is of inestimable value in the borderline type of case as well.

*Corpus luteum hormone.* At one time corpus luteum hormone (progestin, progesterone) was thought to be the cure for menorrhagias, because it was purported to exert a quieting effect on the uterus and it was supposed to be an antagonist to estrogens. This opinion was adopted chiefly because most cases of dysfunctional bleeding had the cystic hyperplastic type of endometrium and all cases were anovulatory, indicating the absence of corpus luteum activity. However, the results of treatment with this substance were just the opposite as shown by Hamblen (24), Gillman (25), Zondek and Rozin (26). They showed that progesterone given in the interval between bleeding periods will aggravate a menorrhagia and even cause bleeding to appear prematurely in normal women. However, Weisbader (27) has recently reported that pregneninoline (a synthetic progesterone) has proved effective in checking functional uterine bleeding. He gives 250 to 350 mg. by mouth in divided doses of 50 mg. daily, to check the bleeding. He then uses 200 to 240 mg. in divided doses, during the second half of the succeeding periods to prevent the recurrence. It is difficult to see the mechanism involved here unless it be by *a*) an inhibitory action on the pituitary, *b*) establishing an endocrine balance causing a relative increase or decrease in the estrogenic level, or *c*) making the endometrium less refractory to estrogen. On the other hand, Gaines (20) and his associates found pregneninoline of no value in functional uterine bleeding. They concluded it produced no suppressing effect on the menstrual cycle. Hamblen (15) used corpus luteum cyclically with estrogen for dysfunctional uterine bleeding. This author is of the opinion that there is no indication for corpus luteum hormone (progesterone, pregnenino-

[2] Synapoidin. Parke, Davis & Co., Detroit, Michigan.

line) in any condition in gynecology or obstetrics.

*Estrogens.* Theoretically, it would seem that estrogenic substances would aggravate an existing bleeding state because of its proliferative action upon the endometrium and because it has been found by earlier investigators that the estrogen is increased at the time of the onset of the bleeding (29). It has been stated "Estrogenic hormones have no place in the treatment of uterine bleeding" (29). Also a recent textbook (30) states "There is no theoretical basis for the administration of estrogens . . . unless the bleeding is associated with endometrial atrophy, which is rare." It has been shown recently in our clinic that estrogens, in large doses, will check either normal menstruation or abnormal uterine bleeding with any type of endometrium (2, 3, 4, 31–34).

It is obvious that the estrogens play an important rôle in the bleeding mechanism, for experimentally, even though both ovaries and the pituitary are absent, bleeding can be induced with their use. All that is necessary to produce bleeding with estrogenic substances is the presence of endometrial tissue, if no more than is found in endometriosis. The absence of estrogens, as the result of oöphorectomy, leads to the development of an atrophic endometrium and cessation of uterine bleeding in the presence of multiple submucosal myomas; this has been shown experimentally in 6 cases in our hospital. The endometrium is atrophic in the pre-pubescent girl. In pregnancy, during which there is a high level of estrogens, there is a period of physiologic amenorrhea. Perhaps there is a level of estrogen above that at which bleeding can not occur and amenorrhea results.

The estrogen level for bleeding may vary in different women because of interrelationships with other hormones or with the natural enzyme systems concerned with estrogen metabolism or because of nervous factors. In some instances it is possible that the estrogen level is lower than that required for bleeding, which may explain the increase of estrogen reported by some investigators at the onset of bleeding. The author has administered large amounts of estrogens and has thereby checked abnormal or normal menstruation at will. Upon withdrawal of the estrogen, the blood estrogen level dropped until uterine bleeding ensued. If the patient was castrated only one bleeding occurred. The bleeding which is noted clinically when continuous doses of estrogens are given, or in cases of which the ovaries are cystic, may be explained by the fact that the blood level of estrogen fluctuates into the critical bleeding level as the result of continuous metabolism of estrogen by the liver, kidney and uterus. However, when uterine bleeding occurs during estrogen administration, a larger dose will cause the bleeding to cease. This is because the blood level of estrogen is again pushed out of the range for producing bleeding (4).

Large contraphysiological doses of estrogen may destroy some aberrant ovarian factor (19). This is similar to the theory of Friedman (35), that small doses of roentgen-ray to the ovaries of women who have irregular bleeding or amenorrhea are beneficial, not because roentgen rays are stimulating, but rather because the rays may destroy some inhibiting factor in the ovaries. This theory is further supported by the fact that Stein and Cohan (36) have treated amenorrhea and sterility by removing surgically the cystic portion of both ovaries, a practice which is not advocated in the light of the present knowledge of the estrogens.

McGinn (9) states that large doses of estrogens are effective in checking and regulating functional uterine bleeding by *a*) raising the blood level above that at which bleeding occurs, hence causing an immediate cessation of bleeding, and *b*) inhibiting the gonadotropic influences of the pituitary and giving the ovary a period of rest, thereby tending to restore permanently normal ovarian function and menstruation. It has been proven by the author that larger amounts of exogenous estrogens (5.0 mg. of diethylstilbestrol daily for 20 days) depress the ovarian function until the ovaries are devoid of follicular cysts (37).

*Combined estrogen and progesterone therapy.* Hamblen (38) and his associates used small doses of 10,000 to 20,000 I.U. of estrogen every day for 14 days followed by 5 I.U. of progesterone for 7 days. Cyclic treatment consisted of the administration of estrogens in the first half of the cycle, and corpus luteum hormone, such as progesterone or synthetic anhydrohydroxy-progesterone, in the second half. By this means, after having checked the bleeding, they maintained an artificial pitui-

tary-ovarian rhythm which would tide the patient over until the normal ovarian-pituitary balance occurred. Large doses of progesterone or anhydrohydroxy-progesterone (400 mg.) were used.

We have used cyclic treatment with estrogen and progesterone in 23 cases and on further study have observed that progesterone is not necessary; also, progesterone is somewhat expensive.

It should always be remembered that in a large proportion of the cases, these menstrual irregularities are but passing episodes in the reproductive period of a woman (9).

*Uterine Bleeding With or Without Myomas*

*Dosage of synthetic estrogen, diethylstilbestrol.* Before medication with estrogens is undertaken, cancer, tuberculosis and other causes of uterine bleeding that require surgery should be ruled out.

*a*) If the bleeding is severe, or has been present over a long period of time, or both conditions are present and the patient is in poor physical condition from the loss of blood, 10.0 to 50.0 mg. of diethylstilbestrol may be injected into the anterior wall of the cervix or given by mouth every 15 minutes until the bleeding stops, which requires 3 to 24 hours. Following this 5.0 to 10.0 mg. should be given daily (9 P.M.) for 30 to 40 days. If bleeding should recur during this time, diethylstilbestrol should again be given every 15 minutes until bleeding ceases, while the 5.0 to 10.0 mg. nightly dosage is continued. *b*) If the bleeding is not severe or prolonged, 5.0 mg. is given daily (9 P.M. for 30 to 40 days. *c*) If the bleeding has ceased or apparently is about to, the patient is given 0.5 mg. of diethylstilbestrol by mouth for 2 days, 3.0 mg. for 2 days, 4.0 mg. for 2 days and 5.0 mg. daily thereafter for 30 to 40 days. By giving diethylstilbestrol in this manner the incidence of nausea is lessened (39).

Within 2 to 8 days after the last dose the patient may spot for 2 or 3 days, bleed for 2 or 3 days and then spot for 2 or 3 days. If the amount of uterine bleeding becomes more than that of normal menstruation, the patient should take one-half of a 5.0-mg. tablet of diethylstilbestrol every 15 minutes until the bleeding is checked (not stopped). Within 14 to 21 days normal menstruation usually returns.

*Nausea.* Diethylstilbestrol frequently causes nausea (94 per cent of our cases), and in some cases vomiting. Nausea has been reduced by giving the drug at 9.00 P.M. and by use of rectal suppositories of 1 to 2 grains of nembutal every 3 to 4 hours. If the use of the drug is continued in spite of the nausea, the patient becomes tolerant within 5 to 6 days. The patient is told that after the first dose she will experience nausea the next morning, but to continue the medication; after the second dose she will be less nauseated, and by the 5th or 6th morning after taking the fifth and sixth doses she will no longer experience nausea. Also 400 mg. of ascorbic acid (vitamin C) is given 3 to 4 times a day (40). In a series of 30 patients the nausea was eliminated entirely in 83 per cent of the cases and partially in 6 per cent of the cases. It is important that non-coated tablets of diethylstilbestrol be used. Eight minutes are required for the non-coated and 8 hours for the coated tablets to dissolve.

Occasionally after this treatment the patient will complain of vaginal soreness, backache and headache, but none of these side effects is as distressing as the prolonged bleeding for which the patient has sought relief (11).

*Results of therapy.* Eighty-six cases of adolescent dysfunctional uterine bleeding have been treated by this method. All are menstruating normally at present. None has had to have a dilatation and curettage, radium, roentgen-ray therapy or hysterectomy.

In 142 cases of dysfunctional uterine bleeding referred to the author, bleeding was controlled with diethylstilbestrol. None has had to have a hysterectomy. All have had from 1 to 19 endometrial biopsies with a Randall curette. Twenty-three women experienced a recurrence of dysfunctional bleeding within 3 years, but in all the condition was controlled with diethylstilbestrol, lipo-iodine and thyroid.

In a group of 15 patients with dysfunctional uterine bleeding, it was necessary to resort to dilatation and curettage followed by hysterectomy to stop the uterine bleeding. These cases were bleeding from mechanical, not dysfunctional causes. On gross and microscopic examinations there were endometrial polypi, intrauterine and submucosal myomas and/or endocervical polypi. No malignancy was found by the pathologist in these cases. In all of the re-

maining patients dysfunctional uterine bleeding was controlled with diethylstilbestrol therapy. Yet, caution should be exercised and if malignancy is suspected, a dilatation and thorough curettage should be done and the endometrial scrapings studied by a competent pathologist.

In 584 charity cases, 34 hysterectomies were performed. These were done because the patients could not return for the treatment, and they usually had from 2 to 10 children depending on them for care.

### RADIUM AND ROENTGEN-RAY THERAPY

These are mentioned only to be condemned, except in a very rare case. *a*) Even in the smallest doses, these treatments have a depressing effect on the ovarian activity, hence in so treating an already malfunctioning ovary, little hope can be held for a satisfactory functional recovery. *b*) Many cases of bothersome bleeding occur in the third and fourth decade of life and the results of radiation are notoriously poor in this younger age group. Randall and Lovelady (41) of the Mayo Clinic reported failure in 40 to 50 per cent of the cases in those age groups. *c*) The dividing line between substerilizing doses and those causing permanent amenorrhea and sterility is so uncertain that not even competent radiologists will guarantee the results. *d*) In those women who regain ovarian function and later become pregnant, the percentage of abortion is unquestionably higher.

The writer has had no experience with low-dosage irradiation to the pituitary and ovaries. There have been some glowing reports (42, 43) as to its success, but the fact remains that its use has not been widespread and we know little of its after-effect.

### SURGICAL THERAPY

*Curettage.* The writer is of the opinion that a hospitalization for curettage should be for patients who are 35 years old or older, and should be done to rule out cancer, tuberculosis and other causes of uterine bleeding. A curettement with a Randall instrument, in the office, is a simple and efficient diagnostic procedure in the younger patients. If malignancy or any cause of uterine bleeding other than ovarian dysfunction is suspected, a dilatation and curettage is indicated at any age.

Medical therapy without complete diagnostic study is contraindicated in women *a*) above 40 in whom a diagnosis of malignancy, polyps or submucous myoma is suspected, and *b*) who are bleeding profusely and whose general condition indicates it is necessary to stop the bleeding promptly.

In women who are bleeding profusely, with or without myomas (fibroids) the bleeding may be stopped in 95 per cent of the cases with large and frequent doses of diethylstilbestrol and when the patient is in an improved physical condition, dilatation and curettage can be made if malignancy, tuberculosis or other condition that requires surgery is suspected.

*Hysterectomy.* Hysterectomy is a comparatively rare procedure since the advent of diethylstilbestrol. In 6 years of private practice it has been necessary to perform but 6 hysterectomies in 1568 private cases. In the charity group the percentage of hysterectomies is about 6 per cent of those reporting for uterine bleeding. Hysterectomy is preferable to radiation before the age of 40 because the ovaries, if allowed to remain *in situ* will assure the patient of some ovarian function for 5 to 6 years.

### SUMMARY

A brief summary has been given concerning the present-day conception of the cause and therapy of dysfunctional uterine bleeding. The endocrine preparations of testosterone, chorionic gonadotropin, progesterone, pregnant mares' serum, and chorionic gonadotropin combined with pituitary extract and a pituitary synergist have been found generally unsatisfactory in the treatment of dysfunctional uterine bleeding. The use of large doses of diethylstilbestrol together with tolerated doses of desiccated thyroid and lipo-iodine has been found to give excellent results in 87 per cent of the cases of dysfunctional uterine bleeding. Progesterone has been unnecessary in any obstetrical or gynecological case seen by us. Radiation, frequent curettage or hysterectomy, have played a minor rôle in the therapy of dysfunctional uterine bleeding. Frequent curettement with a Randall curette, in the office, with repeated studies of the tissue has been helpful in the treatment and diagnosis of dysfunctional uterine bleeding.

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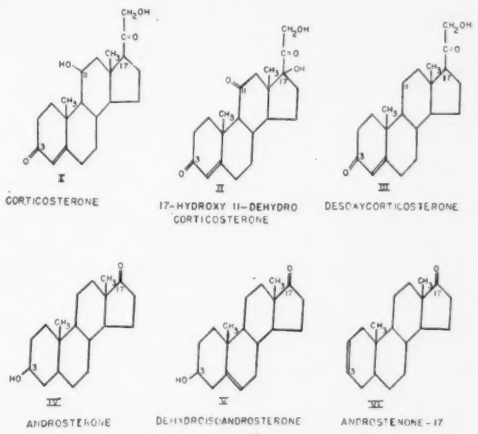
# EDITORIAL

## ADRENOCORTICAL HORMONES IN HUMAN URINE

RECENTLY several papers have appeared presenting evidence that adrenocortical hormones are excreted into the urine of normal men (Dorfman, *et al.*,[1–4]) and particularly into urine of patients after surgical operation (Browne, *et al.*[5,6]). It may be a matter of moment and interest to point out the difference between these substances and other urinary steroids ordinarily considered indices of adrenal function.

Dorfman, Browne and coworkers describe urinary substances having definite corticoid activity by biological assay. The tests they employ are: *a*) the life maintenance of adrenalectomized rats exposed to cold; *b*) the life maintenance of adrenalectomized rats; *c*) the liver glycogen test; and *d*) the muscle work test. It has been demonstrated by numerous experiments that certain steroid substances obtained by the extraction of mammalian adrenal glands will act upon adrenalectomized animals to protect them against the lethal effects of cold exposure, maintain life for long periods at room temperatures, cause the deposition of glycogen in their glycogen-exhausted livers during starvation, and increase the contraction efficiency of the gastrocnemius muscle. Particularly effective in tests *c* and *d* are cortical steroids having an oxygen atom at position 11 on the steroid skeleton, such as corticosterone (I) and 17-hydroxydehydrocorticosterone (II), whereas desoxycorticosterone (III) is especially effective in test *b* and probably effective in test *a*.

Hitherto these and a number of closely related steroid substances have been isolated only from adrenal gland extracts as exemplified in the work of Kendall, Wintersteiner, Pfiffner, Reichstein, *et al.* (for a recent review see Reichstein[7]). The work of Dorfman, Browne and coworkers demonstrates for the first time that these substances are excreted into human urine, and Browne's data especially suggest that they may be excreted in increased amount after surgical intervention. It should be noted that these workers have not identified the urinary material chemically. What they have demonstrated is that a complex mixture of substances extractable from urine by solvents that should remove corticosteroids will exert biological effects similar to those of the adrenal steroids.




Quite different both chemically and biologically are other urinary steroids that have been employed as indices of adrenal steroid production. These are the urinary 17-ketosteroids (for a recent review in this Journal see Pincus[8]). As examples we cite androsterone (IV), dehydroisoandrosterone (V) and androstenone-17 (VI). These typically lack the ketol side chain at C17 characteristic of the hormonally active adrenocorticosteroids (*e.g.*, I, II, III), and also lack the ketone group at C3. They contain 19 carbon atoms where the adrenal substances contain 21 carbon atoms per molecule. The 17-ketosteroids are considered indicative of adrenal cortex activity because *a*) they are lacking or present in very small amount in the urines of Addisonian patients, *b*) they are excreted in very large amount in certain cases with active adrenal neo-

[1] DORFMAN, R. I., B. N. HORWITT AND W. R. FISH: *Science* 96: 496. 1942.
[2] DORFMAN, R. I., AND B. N. HORWITT: *Fed. Proc.* 2: 60. 1943.
[3] HORWITT, B. N., AND R. I. DORFMAN: *Science* 97: 337. 1943.
[4] SHIPLEY, R. A., R. I. DORFMAN AND B. N. HORWITT: *Am. J. Physiol.* 139: 742. 1943.
[5] WEIL, P., and J. S. L. BROWNE: *Science* 90: 496. 1939.
[6] VENNING, E. H., M. M. HOFFMAN AND J. S. L. BROWNE: *J. Biol. Chem.* 148: 455. 1943.
[7] REICHSTEIN, T., AND C. W. SHOPPEE: Vitamins and Hormones. I: 346. 1943.
[8] PINCUS, G.: *J. Clin. Endocrinology* 3: 301. 1943.

plasms, *c*) they are excreted in very nearly normal amount by eunuchs and ovariectomized women, demonstrating only a small contribution to their production by the gonads.

The urinary 17-ketosteroids do not possess measurable corticoid activity in the tests *a*) to *d*) as listed above. They have not been isolated from adrenal tissue. Their chemical constitution suggests that they are metabolic products of more active substances, *i.e.*, they may be reduction products of corticosteroids. They are excreted as esters (detoxified material) whereas the active urinary cortin is apparently not conjugated. The exact precursors of the urinary 17-ketosteroids are not as yet known so that they may be considered as general indicators of adrenal cortex secretion rather than products of specific cortex hormones.

Among the many problems relating to adrenal cortex function the urinary corticoid substance and the 17-ketosteroids should furnish relevant biochemical answers. The extent to which their excretion will vary together or independently should indicate possible types of adrenal secretion in various pathological conditions. A means of ready identification of the urinary corticosteroid may offer new insight into the workings of the complex suprarenal steroid factory. If we can determine also the true precursor substances of the 17-ketosteroids, a formidable diagnostic armamentarium will be available.

G.P.

## PLANT HORMONES

ALTHOUGH the higher plants and animals differ in various superficial respects, in their biological fundamentals they have much in common. Both consist essentially of living cells organized as specialized structures that function in the interests of the organism as a whole. Both begin existence as fertilized ova and go through somewhat similar processes of growth and development. The processes of reproduction also present numerous parallels. In both plants and animals the various organs are integrated into a structural and functional whole. In the animal forms integration is secured largely through the activities of the nervous system but plants are essentially devoid of anything comparable to nervous structures. In both forms, however, chemical control plays an important rôle in integration. Of the chemical integrators in both forms the hormones are the chief members.

While endocrinology has only recently come into the foreground of botanical research, so rapid has been progress in the field that several of the most fundamental problems have been well elucidated. Just as in the animal field, the progress has been attained by the joint efforts of chemists, physiologists, anatomists, pathologists and geneticists. Current knowledge on the subject has recently been brilliantly summarized by Went[1] of the California Institute of Technology.

The hormone is defined by the botanist in terms that would be equally satisfactory to the zoologist. It is "a substance, or chemical messenger, which, transported through the body, determines the growth or function of parts remote from its place of origin. Usually it acts in minute quantities."

Perhaps the simplest example of hormone activity is seen in the control of root growth. This phenomenon depends in part on food elements manufactured by the leaves and in part upon elements obtained directly from the soil. Roots, however, will not grow in merely a food medium. For 40 years it has been known that the addition of yeast extract to the medium results in considerable growth of isolated roots. Within the past decade it has been learned that the most important ingredient of yeast extract is vitamin $B_1$ but other B vitamins also play a rôle. The botanist regards these vitamin substances as true hormones—a conception in which the zoologist might perhaps profitably follow the botanist. It appears, then, that the general root-growth hormone of the higher plants is B vitamin which is produced by the leaves under the influence of light. "It now becomes evident why plants are our best sources of vitamins. They do not produce them for the sake of charity, but are essential factors for their own lives."

Another regulating substance about which much has been learned in recent years is *auxin*, a hormone for stem growth. When the upper part of a young seedling is cut off, stem growth soon diminishes and ultimately stops. If the removed tip is placed again in contact with the stem, growth is resumed. The interposition of a

[1] WENT, F. W.: The regulation of plant growth. *Am. Scientist* 31: 189. 1943.

thin layer of gelatin still permits the growth to go on hence it is due to some diffusable agent, namely the auxin. The auxin of the growing tip can be taken up in agar blocks which also then acquire the property of promoting stem growth. The isolated growth hormone is stable to heat and light and its diffusion rate indicates a molecular weight between 300 and 400. It has been obtained in crystalline form as auxin *b* having the empirical formula $C_{18}H_{30}O_4$. A similar hormone auxin *a*, an excellent source of which is human urine, is structurally identical with the *b* form except that it contains an additional $H_2O$. It is now known that indoleacetic and certain other acids also have physiological properties very similar to the auxins—a theoretical difficulty of a sort not unfamiliar to investigators of animal hormones. Indeed, some writers designate these organic acids as auxins. Went suggests that although the auxin might be thought of as the key which specifically unlocks the door to growth these various acids might be regarded as pass keys. All of these substances have in common an unsaturated ring system with a side chain of at least two carbon atoms adjacent to the double bond and a carboxyl group—or a group readily convertible into a carboxyl group—in the side chain. However, a special configuration between carboxyl group and ring is required—hence structural specificity. Thus "the mental picture which we can make of the growth process is not that of vague stimulation, but rather one in which growth has been brought back into the reality of a chemical reaction."

The botanic endocrinologist has moved ahead of his zoologic confrere by having determined in satisfying detail how the auxins function as growth regulators. They act solely by promoting cell elongation and by increasing the plasticity of the cell wall which then can yield to turgor pressure. In this way auxin controls the growth of stem, leaf stalks and flower stalks, though not that of roots. The responses of plants to gravity and light (geotropism and photopropism) thus fall into line as simple functions under hormone control. For instance when the young, growing stem is placed in a horizontal position more of the hormone seeps into the dependent part with resulting differential increase of growth; this, in turn, causes the stem to bend upward. The auxin distribution having thus become equalized on all sides, growth continues in a vertical direction. The bending of a plant under the influence of light is also explained by the simple fact that on the illuminated side auxin is partly destroyed with a result of relative overgrowth on the dark side. Thus by the effect of gravity and light on the distribution and concentration of the auxin the position of the plants in space in response to their environment is regulated.

What is seemingly a special aspect of the auxin mechanism is the formation of roots on stems of plants, the hormone being produced in leaves and buds and transmitted to the lower part of the stem. The roots being thus initiated, their growth comes under the special control of vitamin $B_1$. The root, in its turn forms a "hormone X" or "caulocaline" which promotes leaf and stem growth. Finally, the development of the ovary into the fruit is also an auxin-controlled phenomenon. It has been found that as an alternative to ordinary fertilization the application of a small amount of auxin to the pistil leads to development of the fruit though not, of course, to the germinal elements—the seeds. Various seedless fruits, such as tomatoes, peppers and watermelons, have thus been produced.

So much for the physiology of the phytohormones. Substantial progress has also been made in the biochemical aspects of the problem. "The most significant advance of recent years in this direction is the discovery of Thimann and co-workers[2] that auxin is part of a respiratory system." It is effective only in the presence of succinic or malic acid, hence, perhaps, serves as co-enzyme in the 4-carbon respiratory cycle and thus contributes to the energy required for growth.

Certain of the genetic aspects of growth and development can be understood in terms of reaction of genes in the hormone activities. It appears that in dwarf corn although auxin production is normal it fails to reach the growing region in adequate amounts. The excessive auxin destruction can be ascribed to the hereditary high oxidative level of the tissues of the dwarfs in which catalase, oxidase and peroxidase are more concentrated than in normal plants. Thus the geneticist and the plant physiologist meet in a common field. Similarly the excessive leaf growth of the cabbage and the excessive flower growth of the cauliflower can be explained as due to hereditary hormone imbalance.

Went concludes, "With the accumulation of more basic data concerning the growth and development of plants, a new science, plant engineering, is slowly emerging. This can contribute materially to a better and more logical utilization of the possibilities which the life activities of

[2] COMMONER, B., AND K. V. THIMANN: On the relation between growth and respiration in the Avena coleoptile. *J. Gen. Physiol.* 24: 279. 1941.

plants offer for our human well-being." It may be hoped that the lag in the application of the newer physiology to profitable horticultural practice will be less than that commonly experienced between experimental endocrinology and medical practice. That this hope is substantial is indicated by the fact that the botanist can experiment directly and radically upon the species in which he is interested—an advantage that is largely denied to the physician.

R.G.H.

*Abstracts of*

# CURRENT ENDOCRINE LITERATURE

*Editor:* DANIEL A. MCGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, EMMERICH VON HAAM, HAROLD WOOSTER.

## BOOK REVIEW

BORRAS, PABLO E.

Temas Endocrines, 313 pp.El Ateneo, Buenos Aires, 1943.

The author, a gynecologist, has developed his book primarily from his own case-history material but has added a section on general endocrinology. The clinical discussion is rather more adequate than the theoretical. The first part of the book deals with the hypophysis and the sex hormones proper. In the literature that is cited the work of Latin-American authors predominates—a feature which adds to the interest of North American readers. The author's ideas as to indications for estrogen and gonadotropin therapy are in part somewhat original. The chapter on the adrenals reports a number of well-studied cases which illustrates the author's conceptions of the underlying pathology. The third part, dealing with the thyroid, avoids the current oversimplification of the subject. The possible multiplicity of thyroid hormones is convincingly illustrated. Certain of the theoretical explanations do not attempt to complete clarity but that fact merely reflects the failure of the whole thyroid problem yet to have advanced to an adequate elucidation. In the final section the endometrium is treated not merely as a responding structure but as an integral element in the endocrine system. The discussion of that topic reports essentially the author's own experimental work.

The book comprises not merely a compilation of literature but presents an account of the author's own experiences and thinking. It is a stimulating volume that deserves the attention of a wide circle of readers though its departure from orthodox teaching will no doubt provoke a certain amount of dissent.—*A.E.M.*

## ADRENALS

BARTELS, E. C.

Treatment of Addison's disease (desoxycorticosterone pellets). *Lahey Clinic Bulletin* 3: 173. 1943.

Eight patients with Addison's disease have been treated successfully with implantation of pellets of desoxycorticosterone acetate. Before implantation of pellets, careful stabilization by injections of desoxycorticosterone acetate was carried out. This permitted an accurate calculation of the number of pellets required. None of the patients suffered the results of overdosage of pellets such as generalized edema with heart failure, headache or hypertension. Perhaps conservatism has led us to use one less pellet in a few cases which therefore resulted in an early return to added injections of desoxycorticosterone acetate. The removal of remaining pellets at some given time, such as a year following implantation, with re-implantation of a fresh supply would alleviate a period of restabilization. This was carried out in 1 case. This would apply only to patients without complications in whom the requirement of pellets most likely would remain the same. The success of pellet therapy is substantiated by the author's experience in successfully carrying patients through illnesses and even surgery. All the patients managed by pellets are carrying out their usual occupation.—*Author's Summary.*

DUBLIN, WM. B.

Relation of structure of adrenal cortex to function in hypertension. *Northwest Med.* 42: 263. 1943.

Normal adrenals, adrenals in a state of nodular cortical hyperplasia with wide variation in com-

bined weight of the glands, nodular disorganization microscopically of cortical architecture, high lipoid content of adrenal cortical cells and single or multiple cortical adenomas reaching a diameter of 2–3 cm. were found in hypertensive and nonhypertensive individuals without more than chance distribution. There appeared, therefore, to be no constant relationship between structure and function of the adrenal cortex in the pathogenesis of hypertension. Material was obtained from 210 postmortem examinations.—*D.A.M.*

## ENDOCRINE GENERAL

ANONYMOUS.

Side-tracking the liver. *Brit. M. J.* 1943: 482. 1943.

Sublingual therapy is now being tried with some success with the sex hormones. Many of these compounds (except, of course, synthetic analogues such as stilbestrol) are relatively ineffective by mouth. But, as Miescher and Gasche have shown, alcoholic solutions of testosterone, methyl testosterone, and estradiol are far more effective in encouraging the growth of the secondary sexual characteristics in castrate albino rats when administered sublingually than when given by stomach tube. This difference may be due, not to inactivation by digestive juices or failure of absorption, but to inactivation of these compounds as they pass by the portal circulation from the intestines through the liver. Burrill and Greene found that testosterone and methyl testosterone were very active when implanted subcutaneously in castrate rats, as judged by the increase in weight of prostate and seminal vesicles over castrate controls. When the pellets were implanted in the spleen, so that the androgens were carried directly to the liver on absorption, methyl testosterone still had a little effect but testosterone was completely ineffective. (Even when orally administered, methyl testosterone is active to some extent, so perhaps the methyl side-chain may delay its destruction by the liver.) If the liver naturally detoxicates these sterols, sublingual administration will side-track the liver, and the sterole will be absorbed directly into the peripheral blood stream. This side-tracking of the liver is an unusual advantage to be claimed for any method of treatment, but there is evidently sufficient value in sublingual therapy for an extensive trial.—*Biol. Absts.*

BIDEN, W. M.

Stilboestrol for breast tumour. *Brit. M. J.* 2: 57. 1943.

In a letter to the Editor, Biden reports the case of a woman of 78 years of age who for 10 years had had a tumor in the upper and outer quadrant of the left breast. Latterly the tumor was offensive and fungating, and appeared to be an adenocarcinoma. There were enlarged nodes in the axilla. Treatment was begun with diethylstilbestrol, in 1 mgm. doses thrice daily to a total of 250 mgm. One month later the tumor appeared to be slightly smaller, and the patient was improving in health. After 3 months the tumor was decidedly smaller, and covered by a thin layer of epithelium. Regression continued, and at the time of writing, 6 months after commencement of treatment, there was a firmly healed nonadherent scar, measuring 3 by 1½ inches, at the site of the tumor. It was unfortunate that biopsy material could not be obtained.—*D.A.M.*

CANTILO, ENRIQUE.

Some remarks about pituitary tonus. *Semana méd.* 50, I: 561, 1943.

This article defends the introduction of the clinical concept of pituitary tonus to avoid expressions like hyper- and hypo-function of the pituitary since standards of normal function do not exist. Illustration is given by the description of the woman of high pituitary tonus with a tendency towards increased sexual function as compared with the hypotonic type with short menses, deficient libido, etc. Neither type is definitely pathological. It is claimed that the various pituitary secretions keep up an approximate parallelism but that the varius glands differ in response. The author defends the point of the intuition of the clinician against the strictly scientific approach.—*A.E.M.*

CATCHPOLE, H. R., AND W. W. GREULICH

The excretion of gonadotrophic hormone by prepuberal and adolescent girls. *J. Clin. Invest.* 22: 799. 1943.

The report covers sixteen series of gonadotropin determinations, each lasting one month. The subjects were 12 girls, in all but one of whom the tests were completed before the menarche, and in 3 of whom menses would not have been expected to appear for several years. The tests were repeated on 4 of the girls after a lapse of one year. In the youngest girls little or no hor-

mone was present, and if present, appeared only after rather prolonged free intervals. In pre-adolescence, gonadotropins occurred more frequently and in increasing quantities. While the amounts might change considerably from time to time, there was no discernible systematic or rhythmic variation. The authors concluded that this hormonal activity is on a "generally lower level than that recorded for the fully developed menstrual cycle." It was their impression that "the pattern of gonadotropic hormone output appeared to be related more closely to developmental status than to chronological age of the subjects."—*T.H.McG.*

COHEN, H. M., D. A. WILSON AND WM. F. BRENNAN

Blood gonadotropic determinations in relation to toxemia of pregnancy. *Pennsylvania M. J.* 46: 1282. 1943.

Studies were made on 119 normal and toxemic pregnant women. Immature rats were injected twice daily for a total of 5 doses with diluted whole blood and ovaries were examined for hemorrhagic follicles and corpora lutea, 96 hours from the first injection. In the 119 cases, 52 were normal, 38 were classified as pre-eclamptic, 1 was eclamptic, 12 were chronic nephritis, 9 were hypertensive from other cases and 7 were unclassified. Of the pre-eclamptics 17 or 44% showed an elevated blood chorionic gonadotropin level over the normal. Of the pre-eclamptics 22 or 56% showed normal blood gonadotropins. Of the other toxemias, including chronic nephritis and essential hypertension, 71% had normal while 29% showed elevated blood gonadotropin levels. Of the normal cases, 85% had normal amounts of gonadotropin and 15% showed elevation. It was concluded that there is only slight correlation between elevated blood gonadotropic hormone levels and pre-eclampsia.—*D.A.M.*

ENGLE, E. T., C. KRAHOWER AND C. D. HAAGENSEN.

Estrogen administration to aged female monkeys with no resultant tumors. *Cancer Research* 3: 858. 1943.

Five aged female rhesus monkeys (Macaca mulatta) were treated with $\alpha$-estradiol administered either as crystals or pellets implanted subcutaneously at intervals of 5 or 6 weeks during a period of 24 to 28 months. The total amount administered ranged from 575 to 825 mg. Histological alterations occurred in the mammary glands of 2 monkeys. Definite cystic changes occurred in the ducts which were diluted to many times their normal diameter. The lining epithelium was normal with no papillary or other proliferation. The acini of glands of all monkeys were normal. Pronounced cystic and glandular hyperplasia of the endometrium was present in 2 animals. The cervic uteri of all animals showed extensive squamous cell metaplasia extending throughout the endocervix and into the racemose glands. No neoplastic changes occurred in any of the organs examined.—*Author's Summary.*

FINKLER, R. S., AND G. M. COHN.

Hormonal effects on growth in children. *Arch. Ped.* 60: 362, 1943.

A group of children ranging in age from 4 to 18 years were treated at the Newark Beth Israel Hospital Endocrine Clinic with appropriate hormonal therapy for growth retardation, cryptorchidism, adiposogenital dystrophy, hypogenitalism, hypothyroidism, simple obesity, malnutrition, mental retardation, behavior problems and menstrual disturbances. The effect upon growth was determined from the Burgess standards of growth rate expectancy. Thyroid (grains $\frac{1}{4}$ to 3 daily for 2 months to 2 years) induced accelerated growth in 14 (58%) of 24 children with hypothyroidism. Marked clinical improvement was noted in the entire group. Anterior pituitary growth extracts (1 to 2 cc. from 2 to 3 times weekly for 2 months to 1 year) produced accelerated growth in 5 (23.8%) of 21 children, some of whom showed benefit during therapy and others in the year after it was discontinued. Most of the children showed a gain in weight and an improvement in vitality. Chorionic gonadotropin (100 to 500 R.U. or 250 to 500 I.U. 2 to 3 times weekly for 3 to 6 months) increased the rate of growth in 37 (63%) of 59 children. Most of the children showed an improvement in genital development, muscular tone and self assurance. Testosterone propionate (10 to 25 mg. twice weekly for 3 to 6 months) caused more rapid growth in 17 (81%) of 21 children. No untoward effects were observed with any of the compounds.—*E.C.R., Jr.*

HUFFORD, A. R.

The synthetic estrogen octofollin (in oil). *J.A.M.A.* 123: 259. 1943.

Octofollin provided prolonged beneficial effects in 21 women with various symptoms indicative

of estrogen deficiency. Therapy was by deep intramuscular injection in doses of 2 to 5 mg. once or twice a week for periods up to 8 weeks. There were no undesirable side effects such as headache, nausea, vomiting, dizziness, breast soreness, pelvic pain or excessive bleeding. Along with general improvement of menopausal symptoms there seems to be a decided diminution of the arthropathies and hypertensions found in the menopausal patient.—*D.A.M.*

LEWIS, R. C., A. M. DUVAL AND A. ILIFF.

Effect of adolescence on basal metabolism of normal children. *Am. J. Dis. Child.* 66: 396, 1943.

From a review of the literature concerned with the basal metabolism of children during adolescence, the authors concluded that there was disagreement whether an increased metabolism occurs at this period of life. On the basis of their own results (1,725 determinations of basal metabolism on 70 boys and 57 girls from 2 to 15 years old, inclusive, made during the past 10 years) they found that: 1) there is no absolute increase at puberty in the mean basal metabolism expressed as calories per hour per square meter in relation to age; 2) there is a relatively increased metabolism during adolescence expressed as calories per hour per square meter with age, indicated by the fact that the rate of decrease of standard values for boys from 11 to 15 years old is only about $\frac{1}{4}$ as great as that in earlier years, and that the rate of decrease of standard values for girls from 10 to 12 years old is only about $\frac{1}{2}$ as great as for younger girls. No correlation was found between the relatively high basal metabolism of early puberty and the time of occurrence of maximal adolescent growth either in weight or in height.—*E.C.R., Jr.*

LEWIS, R. C., A. M. DUVAL AND A. ILIFF.

Standards for the basal metabolism of children from 2 to 15 years of age, inclusive. *J. Ped.* 23: 1, 1943.

The authors present standards for calories per hour per square meter referred to surface area, weight, and height respectively calculated from 1,007 determinations on 70 normal, healthy boys and 718 determinations on 57 normal, healthy girls. Some of the data on which these standards are based have been analyzed elsewhere (*Am. J. Dis. Child.* 53: 348, 1937; 65: 834, 1943; 65: 845, 1943). The authors include scatter diagrams and a comparison between the standards herein reported and certain studies of basal metabolism chosen from the literature.—*E.C.R., Jr.*

LURIE, L. A., S. LEVY AND M. L. LURIE.

Determination of bone age in children. *J. Ped.* 23: 131, 1943.

From roentgenograms the authors have compiled charts of the age appearance and fusion of bone centers in 704 boys and 425 girls ranging in age from $2\frac{1}{2}$ to 19 years. The remainder of a group of more than 2,100 children wer excluded because they suffered from various endocrine disorders or from marked nutritional disturbances. The authors concluded: 1) four roentgenograms (hand including wrist, elbow, pelvis, and foot including ankle) are adequate for determining bone age; 2) films of the lesser trochanter of the femur are frequently distorted and hence unreliable for bone age determinations; 3) a difference of $\frac{1}{2}$ year in age produces neglible variations in osseous development; and 4) girls show a definite acceleration in bone growth as compared with boys. The authors introduce a new term, bone quotient (B.Q.) derived by dividing the bone age by the chronological age.—*E.C.R., Jr.*

PINCUS, G. AND H. HOAGLUND.

Steroid excretion and the stress of flying. *J. Aviation Med.*, 14: 173, 1943.

Human subjects were put under stresses of various sorts and the effects on urine volume and 17-Ketosteroid content determined. The stresses included sessions on a fatiguing "coordination meter" or "pursuit meter," oxygen deprivation and actual airplane flights. Some 300 tests were made. The operations in all groups caused augmented 17-Ketosteroid output and increased urine volume. In the pilot group these increases were proportional to flying time. On the pursuit-meter tests with various grades of oxygen deficiency the increases were correlated with "altitude" and reduction of efficiency of performance. An independent appraisal of fatigability made by the pilots' commander correlated with the degree of ketosteroid and volume increases. It thus appeared that genuine or simulated flying stress caused augmented secretions of adrenal steroid hormones as well as diuresis.—*R.G.H.*

ROBERTS, H. K., ELLEN LOEFFEL AND C. M. MACBRYDE

Octofollin, a new synthetic estrogen. *J.A.M.A.* 123: 261. 1943.

The majority of 44 women obtained relief of vasomotor symptoms of hypogonadism with octofollin by mouth in doses of 5 to 15 mg. daily. Of 26 patients given continuous treatment 15 (58%) obtained good relief of symptoms, 6 (21%) fair, 4 (15%) poor and 1 (4%) no relief. Satisfactory alleviation of symptoms was secured in 11 of the 18 patients given interrupted therapy although they required larger daily doses for the two-week period they were treated during each month than those on continuous treatment. Of the 18 patients receiving 15 mg. daily for two weeks 11 (61%) showed good subjective response while 7 (39%) showed only fair response. Nausea did not occur in any of the patients. A few patients had pelvic discomfort or breast tenderness and pigmentation of the areolae, especially on the 15 mg. daily doses.—*D.A.M.*

SCHNITMAN, SARA AND RAÚL PESINO.

Pubertas praecox. *Semana méd.* 50, II: 172. 1943.

The appearance of premature secondary sexual characteristics occurs more frequently in the female sex than in the male. In the cases presented, the development in girls from 5 to 10 years was only fragmentary, involving either mammary growth or pubic hair and, in one instance, premature bleeding. The appearance of augmented estrogenic hormone in circulation was proved by slightly increased secretion and positive vaginal smears. However these changes are not considered as pathological. The development remains usually stationary until the other sexual characteristics develop at the onset of general puberty. They are on the borderline of pathological precocious puberty.—*A.E.M.*

TORDA, C., AND H. G. WOLFF.

Experimental studies on headache: pharmacodynamics of urine excreted during migraine headache and its relation to 17-ketosteroid content. *J. Clin. Invest.* 22: 853. 1943.

Urine collected during attacks of migraine from each of 12 patients caused the rectus abdominis muscle of the frog to contract to a greater degree than did specimens obtained in migraine-free periods. The rectus abdominis effect was least in the urine collected during prodromal periods. The urine of healthy males and females also exhibited an ability to produce contracture of the rectus abdominis of the frog in a degree comparable to that observed for the urine of migrainous patients collected between attacks. The urine of normal males was 70 per cent more effective than that of normal females. Urine collected in the premenstrual period induced greater contracture of muscle than that excreted subsequent to the menses. The above contracture effects of urine obtained from migrainous patients during attacks was shown not to be due to histamine, acetylcholine, or potassium. It was demonstrated that such urines contained more than the normal amount of 17-ketosteroids, and that the amount of 17-ketosteroid present roughly paralleled the percentile increase in contracture effects of the urine upon the rectus abdominis muscle of the frog. 17-ketosteroids (dehydroisoandrosterone; androsterone; acetate of alpha-hydroxy-etiocholane-17; progestin; progesterone) and other steroids (sodium pregnandiol glycuronidate; testosterone propionate; and cholesterol) were then added to the urines of healthy subjects with an intensification of their ability to cause contracture of the rectus abdominis muscle of the frog. The authors suggest that "steroid compounds may participate in the production of an attack of migraine headache by potentiation of the effect of a locally liberated vasodilator neurohormonal substance." —*T.H.McG.*

## GONADS

DANIELS, G. E.

An approach to psychological control studies of urinary sex hormones. A report on three menstrual cycles. *Am. J. Psychiat.* 100: 231. 1943.

During three sexual cycles a study was made of the gonadotropin, estrogen and 17-ketosteroid output of a normal woman. During the same period psychiatric interviews were held in which a day-to-day account of activities and physical reactions was received. The subject's dreams were also collected and classified. Fairly regular mid-menstrual peaks in gonadotropin output appeared and, iess regularly, augmentation of estrogen. The 17-ketosteroid pattern appeared to be rather random. The subject showed the sort of emotional pattern previously described by Benedeck and Rubenstein. With preovulatory increase of estrogen production there was increased heterosexual tension and frequently euphoria. With ovulation a temporary release of tension and sense of well being were experienced. With the onset of progesterone dominance, tension reappeared but with orientation toward the woman's own body. A desire to become pregnant and, toward the end of the period, to nurse and care for a child was evident. Near the times when

ovulation presumably occurred heterosexual dreams tended to be more numerous and vivid while in the latter part of the cycles dreams involving food, care, pregnancy and interest in children predominated. A critique on this type of research is included.—*R.G.H.*

FULLER, DOROTHEA.

Two new methods of staining vaginal smears. *J. Lab. & Clin. Med.* 28: 1474. 1943.

The author describes a method for staining vaginal smears for the routine study of the menstrual cycle and a second method for differentiating malignant cells. The first mentioned of the two methods demands three staining solutions, but from beginning to end can be completed in from 15 to 20 minutes. Superficial cells stain green; deep cells, a slightly darker green; fully cornified cells appear orange; those less well cornified, pink. The staining of vaginal smears for malignant cells involves a solution which does not keep well, but, if fresh, offers a differential color reaction which identified such structures quickly and with a high degree of accuracy.—*T.H.McG.*

HERGER, C. C., AND H. R. SAUER.

The effect of orchidectomy and stilbestrol in carcinoma of the prostate. *Am. J. Surg.* 62: 185. 1943.

Studied 82 patients for periods of 3 to 12 months. About 50% of patients receiving stilbestrol medication exclusively respond by regression or softening of the prostate. Authors believe that estrogen therapy without castration should be employed in patients particularly in those (1) with operable carcinoma of prostate who refuse radical operation, (2) in patients with moderately advanced lesions but few or no symptoms, (3) in patients with low grade malignant, well differentiated adenocarcinoma with slow progression of the lesion, and (4) in those patients refusing castration or in whom castration is contraindicated otherwise. Castration is recommended in all patients with prostatic cancer in whom metastases are demonstrable or in patients with lesions showing rapid progression. In addition, castration is recommended in patients who do not respond to stilbestrol administration. The value of combined castration and stilbestrol medication is undecided. Most patients who fail to respond to orchidectomy also fail to respond to estrogen therapy. In many patients, however, estrogen therapy in addition to castration may accelerate improvement. It is not believed that castration or stilbestrol therapy results in cures, although such treatment yields more favorable results than palliative X-radiation or interstitial radiation. Neither castration or stilbestrol treatment can substitute for surgical removal of cancer of the prostate in patients in whom the prostate is still encapsulated.—*D.A.M.*

TRABUCCO, A.

Hypertrophy of the prostate, considerations on adenoma of the prostate. *Rev. Assoc. med., argent.*, 55: 98; 455. 1941.

The author discusses the etiology and pathogenesis of the tumor; the physiopathology of urine retention; and the results of endocrinotherapy in adenoma of the prostate. He favors the theory of lack of balance in testicular hormone as the etiological factor and is of the opinion that these adenomas should be regarded as benign growths that readily become malignant. In this connection the author quotes the statistics of Albarran and Hallee in which 14% of the adenomas showed centers of carcinomatous degeneration, and those of Chauvin and Messinger in which 32% showed metaplasia and some true spindle cell carcinomas. Destruction of muscle in the bladder is often connected with urine retention. Testosterone propionate was given to 50 patients, the optimum dose averaging 167 mgm. The symptoms began to subside after an average of 10 to 15 days. If treatment was stopped after the maximum improvement was reached, the symptoms reappeared after an average interval of 30 days. The minimum dose necessary to maintain the improvement was 5 mgm. a week. Dysuria subsided quickly in 21% of the cases, gradually in 15%, slowly in 10%, and hardly at all in 15%. Polyuria disappeared completely in 30% of the patients, was reduced to 1 micturition per night in 23%, and to 2 or more in 15%. Urine retention was completely relieved in 52%, but in these cases it had been mild in the beginning; in the remaining patients it was reduced to half that which it had been before treatment. Endocrinotherapy does not seem to affect the size of the tumor and does not change the symptoms in the second or third phase of the disease. Fourteen illustrations are appended.—*D.A.M.*

## HYPOPHYSIS

ADELSTEIN, L. J.

The management and treatment of pituitary tumors. *West. J. Surg.* 50: 230. 1942.

Irradiation of pituitary adenomas may well be

tried first—before surgical intervention—unless there are special contraindications such as progressive and imminent loss of vision. Postoperatively, roentgen therapy seems definitely to prolong the period before evidence of recurrence appears.—*D.A.M.*

CRANMER, R. R.

Tumors of the pituitary gland. *Minnesota Med.* 25: 38. 1942.

Diagnosis of primary hypophysial tumors is based on: (1) endocrine disturbances; (2) changes in the bones, as evidenced by radiograms, such as enlargement and destruction of the sella turcica, and occasionally an intrasellar shadow; (3) changes in visual fields and eyegrounds; (4) headaches and other signs of increased intracranial pressure. These tumors are treated by surgical intervention and x-ray. Four cases are presented.—*D.A.M.*

## PANCREAS

CORNER, B. D.

Primary carcinoma of the pancreas in an infant aged seven months. *Arch. Dis. Child.* 18: 106. 1943.

The chief features of this case include: (1) abdominal distension with tumor mass starting at age 5 months; (2) abdominal pain, flatulence and vomiting at 7 months; (3) glycosuria; (4) anemia (hemoglobin 40%); (5) fasting blood sugar 113 mg.%, cholesterol 109 mg.%; (6) mild fever; (7) lack of malnutrition; and (8) adenocarcinoma of head of pancreas invading the liver found at laporotomy and removed at post-mortem; metastases to anterior mediastinal lymph nodes, pleural surfaces of both lungs, and liver; extension of tumor into many branches of portal vein. —*E.C.R., Jr.*

FELSEN, J., W. WOLARSKY AND E. ROSEN.

Cystic fibrosis of the pancreas in siblings, with necropsy reports. *Arch. Ped.* 60: 488. 1943.

Two cases of this condition are described in siblings born one year apart with death occurring on the sixth and twenty-seventh days of life. This report constitutes the fourth recorded instance in siblings. Necropsy findings are presented. The authors suggest that the condition be suspected in the newborn siblings of those who have had the disease and that they be given from the day of birth pancreatic ferments and vitamin A by mouth and by injection as preventive therapy; mothers of such children should be given vitamin A throughout pregnancy.—*E.C.R., Jr.*

JOSLIN, E. P.

Diabetes mellitus. *New Eng. J. Med.* 228: 645. (May 20) 1943.

This is a general review article on medical progress in diabetes mellitus. Statistical data are presented to show the break in the upward curve of mortality from diabetes mellitus from 1941 onwards. Diabetic dwarfism is discussed and the incidence of retardation among 1,407 diabetic patients with onset of the disease under fifteen years of age was 8.3 per cent. The characteristics of 4.6 per cent of the entire series of juvenile diabetic patients and 55 per cent of the retarded group were stunted stature, abnormal proportions, delayed differentiation and hypogenitalism. Thyroid extract, parenteral anterior pituitary extract and testosterone stimulated growth in typical diabetic dwarfism. The increased severity of diabetes that followed endocrine therapy was evaluated and it was concluded that the social and economic importance of the problem outweighed the danger resulting from increase in severity of diabetes which could be controlled by an increase of insulin. The role of the adrenal glands in carbohydrate metabolism is discussed. Adrenalin, the active principle of the adrenal medulla, leads transitorially to hyperglycemia and glycosuria. This is accompanied by the conversion of glycogen in the liver into sugar and its discharge into the blood stream, thus opposing insulin, which promotes the formation of glycogen in the liver and muscles. Amongst the various hormones of the adrenal cortex there are hormones controlling the distribution of inorganic ions and permeability of membranes and others that affect glucose formation and deposition of glycogen in the liver. Desoxycorticosterone belongs to the former group and has no effect on carbohydrate metabolism, whereas the latter hormones belong to the corticosterone series and control not only carbohydrate metabolism but also electrolyte balance. In adrenal insufficiency, carbohydrate metabolism is disturbed in three ways: there is an increased oxidation of glucose in the peripheral tissues (muscles); the liver and kidney fail to synthesize glucose from tissue protein, amino acids and lactic and pyruvic acids; and hypoglycemia is present, as well as a failure of the liver to convert glucose to glycogen. The manner in which the cortical principles inhibit the utilization of carbohydrate is not known. The problem of pregnancy complicating diabetes is also

discussed. One hundred and twenty-five consecutive pregnancies were studied. The fetal mortality was 12 per cent. The maternal mortality was 0.8 per cent. Oversize was a characteristic of infants of diabetic mothers. Weight was influenced by body fat, edema and splanchnomegaly. Congenital defects were found in 17 per cent of the 125 cases. Maternal course was abnormal. Forty-two per cent of the 125 mothers had toxemia, and 25 per cent delivered prematurely. Only 0.8 per cent had diabetic coma and only 0.8 per cent had severe hypoglycemia. Fetal wastage and an abnormal clinical course could not be correlated with congenital defects or the disturbed chemistry of diabetes, but both occurred with an imbalance of the hormones of pregnancy. Forty-one of the patients had a normal balance of the hormones of pregnancy and 84 had an abnormal balance. When the hormonal pattern was normal the fetal survival was 95 per cent, the incidence of toxemia 2 per cent and premature delivery 0. When the pattern was abnormal the uncorrected fetal survival was 60 per cent, toxemia 52 per cent and prematurity 40 per cent. When corrective treatment was employed (diethylstilbestrol in doses of 10 to 50 mg. daily and Proluton in doses of 5 to 40 mg. daily were used most commonly) the toxemias were modified, the fetal survival was 92 per cent and prematurity 18 per cent. Corrective substitutional therapy, therefore, modified the abnormal maternal course and raised fetal survival to more than 90 per cent. *R.B.G.*

KAUFMANN, W., AND D. B. CHAMBERLIN.

Congenital atresia of pancreatic duct system as a cause of meconium ileus. *Am. J. Dis. Child.* 66: 55. 1943.

The authors report a rapidly fatal case of miconium ileus in a 3-day old infant due to complete maldevelopment of all intrapancreatic ducts, ductules and acini; an anomaly not previously described as a cause of this syndrome. They concluded that this anomaly or any obstruction of the large pancreatic duct prevents the exocrine secretions of the pancreas from reaching the intestine, and hence from digesting the fats and proteins in the meconium; as a result inspissation and hardening will occur so that fatal intestinal obstruction results.—*E.C.R., Jr.*

LURIE, L. A., AND S. LEVY.

Pancreatic encephalopathy. Review of literature, with report of a case. *Am. J. Dis. Child.* 66: 49. 1943.

The authors observed a white girl of 14 years who: (1) had intermittent attacks of abdominal pain, nausea, and vomiting for 8 years; (2) abruptly developed an acute toxic psychosis characterized by agitation, confusion, disorientation, lack of insight and judgment, auditory and visual hallucinations, delusions of persecution, shallow emotional reactions, slurring speech, perserveration, stereotypy, compulsive actions, intermittent lucid intervals, rigidity of facial muscles with mask-like expression, fine tremor of tongue and hands, cogwheel spasticity of extremities, hyperactive tendon reflexes, absent abdominal reflexes, and normal plantar reflexes; and (3) suddenly and spontaneously recovered without residuals. Because she was underweight, underheight and premenarchal the authors suggested that she might have Lorain-Levi type of pituitary dystrophy. However, it was concluded that she had pancreatic encepholopathy because of the similarity of her case to 8 reported by Rothermich and von Hamm (*J. Clin. Endocrinol.* 1: 872. 1941) with changes in the pancreas consisting "of more or less sharply circumscribed areas of fatty or glandular necrosis and a marked periductal fibrosis with dilatations of the medium-sized and smaller ducts and epithelial proliferations with metaplasia," as well as "severe interstitial fibrosis leading to atrophy of the glandular tissue." Brain lesions consisted of focal areas of capillary hemorrhage, perivascular edema and reactive gliosis with occasionally atrophy of the cortex. The importance of recognizing in children encephalopathies due to somatic disease is stressed.—*E.C.R., Jr.*

MADDOCK, C. L., S. FARBER AND H. SHWACHMAN.

Pancreatic function and disease in early life. II. Effect of secretin on pancreatic function of infants and children. *Am. J. Dis. Child.* 66: 370. 1943.

This report concerns 26 determinations on the duodenal content of 21 infants and children before and after injection of secretin. The subjects included normal individuals, and patients with celiac disease, chronic nutritional disturbance, pancreatic fibrosis and selective trypsin deficiency. It was found that: (1) secretin may be repeatedly injected intravenously into such subjects without ill effects or danger; (2) in normal individuals and in patients with celiac disease or chronic nutritional disturbance secretin increased the volume and pH of the duodenal content; (3) in 7 patients with pancreatic fibrosis secretin

produced no important change in either volume or tryptic activity; (4) in a boy with trypsin deficiency secretin induced an increase in volume, in lipolytic and in amylolytic activity, but no change in tryptic activity; (5) secretin induced an increase in lipolytic activity in all subjects except those with pancreatic fibrosis in whom a slight decrease was observed; and (6) secretin induced an increase in amylolytic activity in all subjects except those with pancreatic fibrosis and with celiac disease in whom a slight decrease was observed.—*E.C.R., Jr.*

MacBryde, C. M., and H. K. Roberts.

A new modified protamine zinc insulin: comparison with histone zinc insulin, clear, and standard protamine zinc insulins. *J. Clin. Invest.* 22: 791. 1943.

This study was prompted by a desire to obtain a modification of insulin capable of controlling the tendency to a mid-morning rise in blood sugar, and of sustaining its action steadily through the rest of the day and night. The preparation used by the authors consisted of equal parts of protamine zinc insulin and regular (unmodified) insulin with buffer added to bring the pH to 7.2. Assay of this particular mixture demonstrated that 75 per cent of the insulin was precipitated, and 25 per cent was soluble. This ratio of 3 to 1 was selected after a critical evaluation of the data in 57 ambulatory patients who had required combined therapy with separate daily injections of protamine zinc insulin and regular insulin, the proportion in more than half lying between 2.5:1 and 3.5:1. The activity of this "3:1" insulin was compared with that of histone zinc insulin, clear protamine zinc insulin (pH 3.3 to 3.5), and turbid protamine zinc insulin (pH 7.1 to 7.2—market) with or without separate supplemental injections of regular insulin, in patients whose diabetes was fully stabilized under hospital conditions on a constant regime of diet, activity, and insulin dosage. Each patient served as his own control, being successively placed upon equivalent amounts of each of the insulin regimes to be tested. From 4 to 7 days after stable blood sugar levels were obtained in each instance, a "24 hour blood sugar curve" was determined. The blood sugar was estimated at 7:30 (fasting) and 10:30 a.m.; at 2:30 and 7:30 p.m.; and at 12 midnight. All specimens except the fasting were designed to represent the level existing approximately 2½ hours after a feeding. When the curves obtained for these determinations were compared, both in the individual and in the composite, the following results were apparent: (1) In 18 patients receiving histone zinc insulin, control of the diabetic was not as good as with turbid protamine zinc insulin with or without supplemental regular insulin; the fasting level was higher; the mid-morning rise was unaffected (others have claimed a rapid action); and the evening and night blood sugars averaged 20 mgm. per cent greater than with the protamine zinc insulin. (2) In 11 patients receiving clear protamine zinc insulin, the fasting and mid-morning blood sugars were higher than on protamine zinc insulin; there was a tendency to hypoglycemia with shock in the mid-afternoon, and a return to excessively high levels during the night. (3) In 11 patients, "3:1" insulin compared favorably with protamine zinc insulin with or without separate supplemental injections of regular insulin in that (a) the mid-morning hyperglycemia did not occur; (b) the 2:30 p.m. blood sugar was lower; and (c) the night levels were approximately the same. The authors conclude that multiple forms of insulin are not necessary and believe their use should be discouraged. They suggest that regular insulin should be used for emergency purposes, and that a modified form of protamine zinc insulin such as that they have described should be employed in the control of uncomplicated cases of diabetes.—*T.H.Mc.G.*

Miller, H. C., and H. M. Wilson.

Macrosomia, cardiac hypertrophy, erythroblastosis, and hyperplasia of the islands of Langerhans in infants born to diabetic mothers. *J. Ped.* 23: 251. 1943.

Cardiac enlargement was demonstrated by roentgenography in 10 infants born to women with diabetes mellitus at the New Haven Hospital. The enlargement was marked shortly after birth, but disappeared completely 6 weeks thereafter. Post-mortem data on 18 babies born to diabetic mothers were compiled from the literature, and from the New Haven Hospital, the New York Hospital and the Boston Lying-in Hospital. Macrosomia (more than 3,900 grams) was present at birth in 9; cardiac hypertrophy in 8/9 of the heavy and 1/9 of the light infants; hyperplasia of the islands of Langerhans in 6/9 of the heavy and 4/9 of the light babies; and excessive amounts of hemopoietic tissue in 6/9 of the heavy and 2/9 of the light infants. All 4 abnormalities were found associated in 3 infants. Two of the mothers became diabetic after; the others were diabetic before the birth of the

autopsied infants. No correlation could be obtained between the findings in these infants and the blood sugar levels of either the infants or the mothers. It is suggested that: (1) the morbidity of these infants during the first few days of life may be due to the cardiac hypertrophy; (2) the cardiac hypertrophy may be due to excess glycogen deposition in the myocardium; (3) the anatomical picture is similar to that observed in infants with erythoblastoma fetalis born to nondiabetic women (however, all the diabetic mothers tested were Rh positive); and (4) serial roentgenograms may be of diagnostic importance in newborn infants.—*E.C.R., Jr.*

SHWACHMAN, H., S. FARBER AND C. L. MADDOCK.

Pancreatic function and disease in early life. III. Methods of analyzing pancreatic enzyme activity. *Am. J. Dis. Child.* 66: 418. 1943.

The authors describe in detail methods used originally by others and offer a critical evaluation of them based on experience gained from analysis of the duodenal drainage obtained from over 150 infants and children.—*E.C.R., Jr.*

SHOHL, A. T., C. D. MAY AND H. SHWACHMAN.

Studies of nitrogen and fat metabolism on infants and children with pancreatic fibrosis. *J. Ped.* 23: 268. 1943.

Metabolic studies have been performed on 9 children with pancreatic fibrosis and 6 children with other chronic diseases as controls. The ages of 13 ranged from 5 to 19 months; one child was 4, another 11 years old. Collections were made in 3 to 5 day periods; the nitrogen content of the food, urine and feces, and the fat content of the feces were determined. The effects of various feeding regimes were studied. The authors found that patients with pancreatic fibrosis: (1) have a type of metabolism which closely approximates that described in dogs with blocked pancreatic ducts characterized by feces with high residue, large nitrogen and moderate fat content; (2) when fed a diet containing nitrogen but no native protein (a mixture of casein hydrolysate, dextrimaltose, starch, olive oil, brewer's yeast, and salts) showed little change in the dry weight, nitrogen and fat content of the feces; (3) when given pancreatin and a diet containing both protein and fat exhibited some reduction in the amount of nitrogen content but no change in the fat of the feces; and (4) when given intravenously (or fed) a fat-free ration of casein-hydrolysate and glucose showed a reduction to within normal limits in the amount the nitrogen content and the fat of the feces. The authors point out that: (1) pancreatin did not improve the fat metabolism, perhaps because available preparations are low in lipase; (2) good nitrogen retentions with the fat-free ration were probably due to the absence of fat rather than to the method of administration; (3) the presence of fat in the stools when no fat was given raises the question as to the nature of fat and its endogenous production in these cases; and (4) hydrolyzed casein plus carbohydrate is utilized in generous amounts by these patients and in combination with pancreatin (to make good the enzyme deficit) seems to offer improved dietetic therapy.—*E.C.R., Jr.*

## PARATHYROID

MEYER, K. A., AND A. B. RAGINS.

Carcinoma of the parathyroid gland. *Surgery* 14: 282. 1943.

This is a detailed presentation of a case of carcinoma of the parathyroid gland with postmortem findings. Extirpation of the tumor some 26 months before death was followed by only temporary improvement in the objective and subjective symptoms. Eight months following the operation, the subjective symptoms reappeared, and a year later the fibrocystic changes of the bones became progressively worse, despite x-ray irradiation to tumor mass and bone. This was followed by a number of pathologic fractures. Six weeks before death the serum phosphorus rose to 10 mgm. indicating renal decompensation. The essential findings of the postmortem examination were as follows: recurrent carcinoma of the parathyroid gland with metastasis to the peritracheal, subclavicular and perijugular lymph nodes, the lungs and the right kidney; generalized osteitis, fibrosis cystica of the bones; bilateral nepholithiasis, bilateral chronic ascending pyelonephritis, left pyonephrosis with atrophy of the renal cortex and nephrocalcinosis. —*From Authors' Summary.*

ROYDE, C. A.

A case of osteitis fibrosa cystica with parathyroid tumor. *Brit. J. Surg.*, 30: 118. 1942.

A case of severe hyperparathyroidism is described, with a full account of the blood chemistry. The effect of operation is noted and the histologic appearance described. The 53-year-old female patient showed a considerable generalized

decalcification of bone, with numerous cysts and two pathologic fractures. The blood chemistry was within normal limits except for a gross increase of plasma-phosphatase. The urinary excretion of calcium was definitely below normal. Latent tetany developed postoperatively; it was controlled by calcium administration, the dosage being determined by means of the Sulkowitch test. Sections of the parathyroid gland showed a generalized hyperplastic adenoma. The cystic areas of bone presented the typical microscopic appearance of osteoclastoma. The kidneys showed mild ischemic nephritis with small areas of calcification in some of the vessel walls. All of the other organs were normal at autopsy. Literature relating to the mechanism of parathyroid function is reviewed briefly and the pathogenesis, histology, symptoms and treatment of osteitis fibrosa cystica are discussed. The bearing of kidney damage on prognosis is pointed out and the need for examination of kidney function in detail in any case of osteitis fibrosa cystica is emphasized.—*D.P.*

## THYMUS

POER, D. H.

Effect of removal of malignant thymic tumor in a case of myasthenia gravis. *Ann. Surg.* 115: 586. 1942.

The removal of a malignant tumor of the thymus in a case of myasthenia gravis is recorded and the literature bearing on the association of thymic lesions with myasthenia gravis reviewed. In a total of 129 autopsies and operations performed in cases of myasthenia gravis, thymic lesions in the form of persistence, enlargements or tumors have been found in 71 instances. During the past five years, pathologic changes in the thymus have been found in over two-thirds of the cases of myasthenia gravis in which the thymus was examined at autopsy or operation. In the author's case, removal of the thymic tumor was followed by marked clinical improvement. These facts, together with the favorable results noted by Blalock, Harvey, Ford and Lilienthal (J. A. M. A. 117: 1529. 1941) following removal of one thymic tumor and six thymic enlargements, are cited as evidence that the thymus is definitely concerned with the etiology of myasthenia gravis. The necessity of close investigatiion of thymic function in every patient with this disease is emphasized.—*D.P.*

## THYROID

ASTWOOD, E. B.

Treatment of hyperthyroidism with thiourea and thiouracil. *J. Am. Med. Assn.*, 122: 78. 1943.

The daily administration of 1 to 2 gm. of thiourea or of 0.2 to 1 gm. of thiouracil to hyperthyroid persons resulted in the relief of symptoms and the return to normal of the serum cholesterol and the basal metabolic rate. There were observed a latent period of one to two weeks before these effects occurred, a sustained remission during treatment, and a return of hyperthyroidism when therapy was discontinued.—*Author's Summary.*

ASTWOOD, E. B.

The chemical nature of compounds which inhibit the function of the thyroid gland. *J. Pharmacol. and Exp. Therap.* 78: 79. 1943.

The relative effectiveness of 106 chemical compounds in inhibiting the function of the thyroid gland was tested in young rats. When these substances were administered in the food or drinking water for a period of ten days, the degree of thyroid hyperplasia, as estimated by gross and microscopic examination, provided an estimate of their activity. Two classes of compounds were found to be active: thiourea derivatives and certain derivatives of aniline. The compounds more effective than thiourea in decreasing order of activity were: 2-thiouracil, 2-thiobarbituric acid, sym.-diethylthiourea and 5-benzal-2-thiohydantoin. The effective aniline derivatives comprised the sulfonamides, p-, m-, o-aminobenzoic acids, p-aminophenylacetic acid and p-aminoacetanilide. Thiocyanates were found to cause thyroid enlargement only in the absence of added iodide, while organic cyanides failed to influence the thyroid gland.—*Author's Summary.*

ASTWOOD, E. B., J. SULLIVAN, ADELE BISSELL AND R. TYSLOWITZ.

Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat. *Endocrin.* 32: 210. 1943.

The administration of certain sulfonamides, or of thiourea, to normal rats resulted in an enlarged, hyperemic and hyperplastic thyroid gland, coincident, with a state of hypothyroidism as indicated by decreased food intake, decreased growth and development and by lowered basal oxygen consumption. The thyroid hyperplasia

was not influenced by large supplements of iodine, but was bolished by the administration of thyroid powder and by hypophysectomy. The calorigenic action of thyroid powder in normal or in hypophysectomized rats was not inhibited by these compounds. The goiterigenic activity of the compounds tested decreased in the order: thiourea, sulfadiazine, sulfapyridine, sulfathiazole, sulfaguanidine, sulfanilylurea, sulfanilamide and sulfasuxidine. The thyroid hyperplasia which occurs under the influence of these drugs is considered to be compensatory to the failure of thyroid hormone synthesis.—*Author's Summary.*

BRAM, I.

The medical management of exophthalmic goiter: end results in three thousand cases. *M. Rec.* 156: 345. 1943.

Because of the resistance of exophthalmos and other symptoms of Graves' diesase to thyroidectomy, the author believes that the management of this disease requires a "broad modern psychosomatic approach." The drugs used are quinine, iodine as iodized calcium, prostigmin, the barbiturates, and in extreme underweight, insulin. Desiccated thyroid is used when the thyroid swelling has reached the colloid stage. Psychotherapeutic means are also suggested. Of the 3,000 cases followed up in person, 88% are normal insofar as Graves' disease is concerned. The remaining 12% present mild sequelae which do not interfere with their normal social usefulness. —*H.W.*

BROWN, E. E., AND V. P. WASSON.

Basal metabolism in rheumatic children. *J. Ped.* 23: 19. 1943.

An analysis is presented of 154 basal metabolism tests on 97 ambulant rheumatic children. It was found that: (1) the average metabolic rate of all patients was below normal (−7.6%); (2) there were 43 with at least one reading below −10%, while only 2 were above 10%; (3) seasonal variations occurred with values tending to approach normal from July to December, and to decrease below normal during the rest of the year; and (4) the skin and hair of many rheumatic children tended to become dry in the winter and the spring and to improve in the fall (the authors point out that this may be correlated with seasonal changes in the activity of the thyroid gland). The authors suggested that the decreasing metabolism from January through June may be due to the toxic effect produced by the infection on the thyroid gland during and immediately following the season of greatest rheumatic activity.—*E.C.R., Jr.*

CARTER, G. S., F. G. MANN, J. HARLEY-MASON AND G. N. JENKINS.

Paraxanthine as a natural anti-thyroid substance. *Nature.* 151: 728. 1943.

Previous work has shown that the rate of beat of the frog's heart differs in its response to temperature in winter and in summer. Addition of thyroxin to the perfusion medium causes a "winter heart" to behave like a "summer heart." Many antithyroid substances are known, and an antagonistic material present in mammalian liver and in urine was found to convert "summer hearts" into "winter hearts." Prolonged fractionation led to the isolation of this substance and its identification as paraxanthine (1, 7-dimethylxanthine). Various related substances are inactive. Oral administration of paraxanthine in small amounts to the rat lowers basal metabolism. As the dose is increased beyond 20–25 γ per day to a 200–250 gram rat, basal metabolism rises so that finally at about 50 γ per day the normal rate is restored. Additional dosage then gives no effect. When a rat receives more than the maximally effective dose of paraxanthine, thyroid administration *lowers* the basal metabolism. In normal individuals, since thyroxin raises the rate of basal metabolism and paraxanthine lowers the rate, the quantity of the latter substance is clearly below the amount producing minimum metabolism at a normal thyroid level. Paraxanthine can, however, be detected in blood in quantities believed to be physiologically effective, so that the substance has to be considered as a normal part of the mechanism regulating the metabolic level. It is, however, not yet known if the paraxanthine level of the blood can be altered by the organism in a way comparable to the regulation of the thyroid secretion.—*G.E.H. in Am. Scientist.*

CATTELL, R. B.

Operation for carcinoma of the thyroid of lateral aberrant origin. *Surg. Clin. North America* 22: 681. 1942.

All patients with lateral aberrant thyroid nodules should be operated upon. If the tumor appears to be discrete and single, its removal together with the lymph nodes immediately adjacent can be carried out. If the lymph nodes are not involved and the homolateral lobe of the thyroid

gland has no involvement, this procedure should give a good result. If multiple nodules are present, or if the thyroid lobe on the same side of the neck is involved, a more radical operation is indicated. Under these circumstances a diagnosis of carcinoma of the thyroid of lateral aberrant thyroid origin must be made. A radical dissection of the neck, particularly of the lower two-thirds, should be carried out in the presence of these findings, and postoperatively these patients should receive adequate x-ray therapy. The technic of the procedure employed by the author is outlined.—*D.A.M.*

DRILL, V. A., AND C. B. SHAFFER.

Serum cholesterol, serum phosphatase, and bromsulphalein retention in experimental hyperthyroidism. *Gastroenterology* 1: 308. 1942.

Nine dogs on a standard diet plus varied supplements of vitamin B were fed from 0.4 to 0.6 gm. desiccated thyroid substance per kilogram of body weight per day for periods up to 120 days. Frequent concomitant determinations of serum cholesterol, bromsulphalein dye retention, and serum phosphatase were carried out to a total of 71 estimations of each of the two latter. The retention of bromsulphalein above 15 per cent in 30 minutes by the technic used was considered as evidence of abnormal liver function. Elevations of serum phosphatase (above 5 Bodanski units) were observed whenever bromsulphalein was not normally excreted, the serum values of the dye and the enzyme closely paralleling each other in the hyperthyroid state. Serum cholesterol values were not significantly affected. Dietary supplements of vitamin delayed the onset of liver damage but did not prevent it. As a result of their observations, the authors consider serum phosphatase a sensitive indicator of liver damage in hyperthyroid dogs.—*T.H.McG.*

LEWIS, R. C., A. ILIFF, AND A. M. DUVAL.

The comparative accuracy of the closed circuit bedside method and the open circuit chamber procedure for the determination of basal metabolism. *J. Lab. & Clin. Med.* 28: 1238. 1943.

In 65 tests on 36 children (19 boys and 17 girls) between the ages of 2 years, 8 months, and 15 years, 3 months, and 55 tests on 25 adults (8 men and 17 women), a close correlation was found between the basal metabolism determined by use of an open circuit chamber method and that estimated by a closed circuit bedside apparatus. The authors consider the previously determined standards of the Child Research Council of Denver as adaptable for a portable closed circuit apparatus as for the open circuit chamber. The importance of obtaining a child's full confidence before estimating its basal metabolic rate is stressed.—*T.H.McG.*

LOUP, ENRIQUE B.

Transplantation of the thyroid in a case of myxedema. *Semana méd.* 50, II: 285. 1943.

The patient was a woman of 22 years showing all the signs of myxedema with an obesity resembling that in Froehlich's syndrome. The body size was 139 cm., the B.M.R. −42.7%. The donor had a diffuse goiter with nervousness, tachycardia and B.M.R. +33%. Lugol treatment had a slightly favorable influence but the tachycardia increased. Subtotal thyroidectomy was performed and two small pieces of the gland were transplanted into the rectus muscle of the first patient. The response was spectacular. The myxedema disappeared within 36 hours and the psychic inertia disappeared completely. The improvement still persisted after six months.—*A.E.M.*

# ASSOCIATION NOTICE

THE Council of the Association is now considering a plan for holding an annual meeting in Chicago in June 1944. Further details will be published in this place as soon as they are available.

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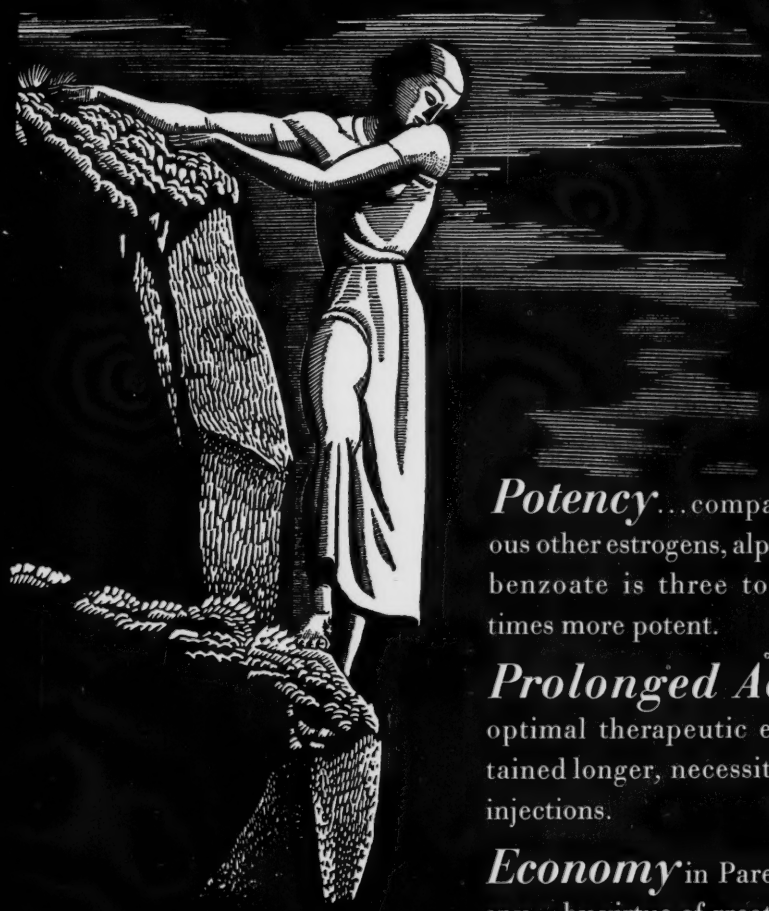

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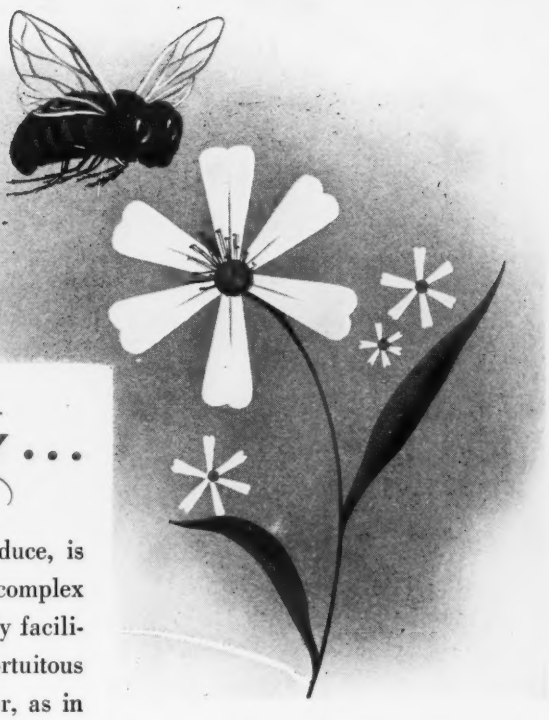

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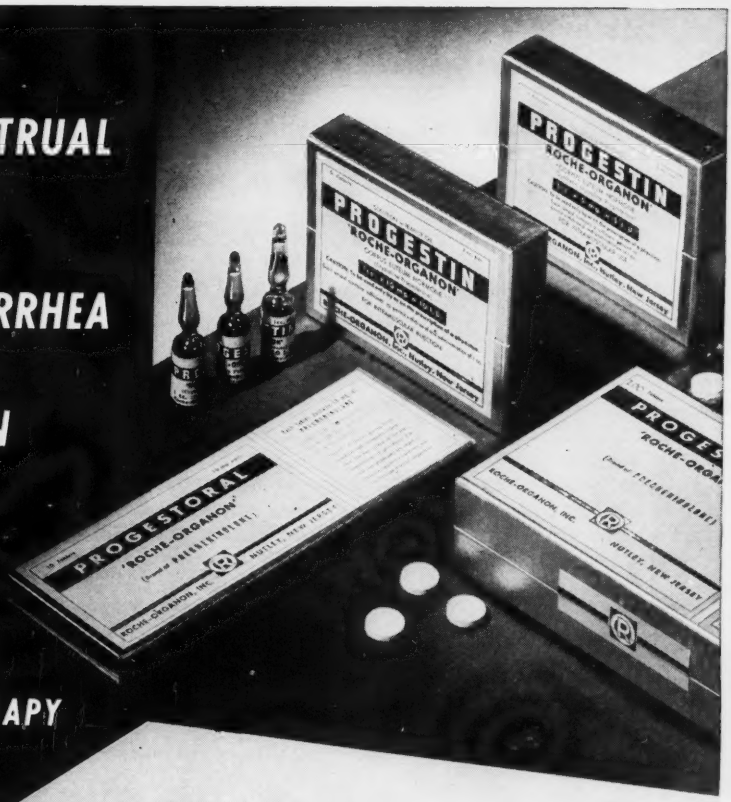


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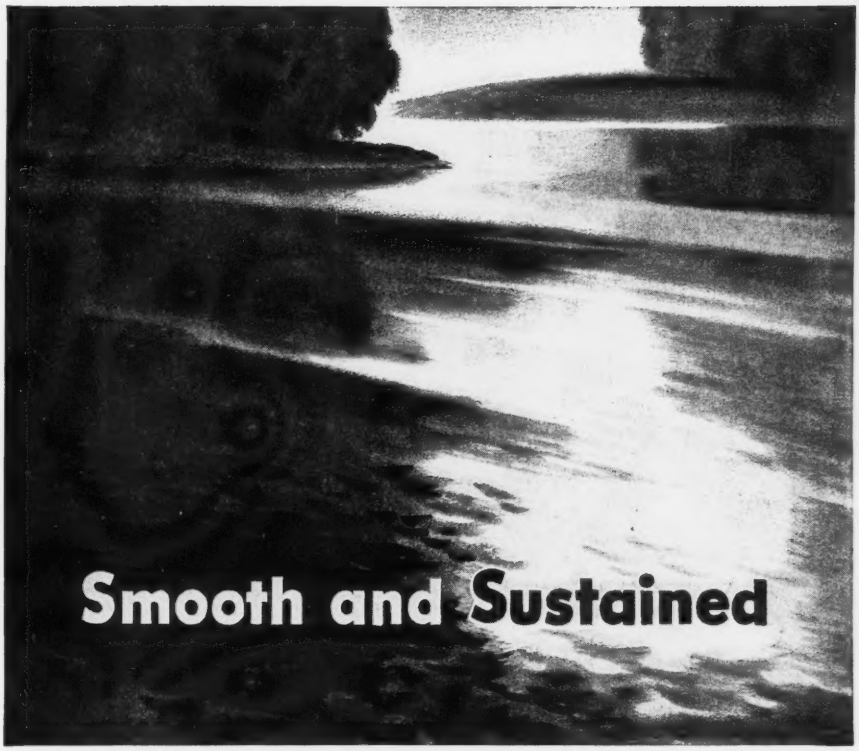


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